ADHD in Danish children and adolescents

Incidence, validity, psychiatric comorbidity, and antisocial outcomes

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BY
CHRISTINA MOHR JENSEN

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AALBORG UNIVERSITY
DENMARK

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Dissertation submitted

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CV

Througout my student years I worked with adults with intellectual disabilities and psychiatric disorders giving me an invaluable insight into the challeges and successes experienced by these people on an everyday basis. This work was followed by an employment in psychiatry at Aalborg University Hospital where I was fortunate to learn about child and adolscent psychiatry including research methods and in particular, to learn about ADHD. Finally, during the last couple of years I have been able to use my knowlegde and skills in the *Love In Chaos* parent-training programme, and to teach and supervise in local schools who hold the important job of developing and stimulating children and adolescents with either psychiatric disorders, disabilities, or who come from difficult social back-grounds.

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ENGLISH SUMMARY

The most frequent reason for referral to the child and adolescent psychiatric hospitals in Denmark is the suspicion that a child or an adolescent may have Attention-Deficit/Hyperactivity Disorder (ADHD) [1]. The core-symptoms of this disorder are patterns of inattention, hyperactivity, and impulsivity, which are atypical given the child's age [2]. Various studies have followed children with ADHD longitudinally into adulthood and have found that these children are at risk for obtaining lower educational levels, have an increased risk of engaging in criminality, developing other psychiatric disorders, and even have higher mortality rates than non-ADHD controls [3-9].

Even though children and adolescents with ADHD share some characteristics with respect to their behaviors and level of functioning, they also have different cognitive, familiar, and social resources available. According to international studies, these individual differences are prognostically relevant, implying that they determine the individual child's risk-profile and to some extent, predict their later outcome [4,6,10-14]. Even though child and adolescent psychiatric departments are mainly focused on treatment of ADHD at presentation, there is also the more far-reaching aim to minimize the impact of the diagnosis on the later developmental outcome of the child. Therefore, knowledge of the characteristics of Danish children and adolescents with ADHD and their family and social background are important and targeting these characteristics in treatment and preventive work could prove beneficial.

A large body of international research has contributed to our knowledge about the impact of ADHD across the lifespan, but there is still a need for improving knowledge about outcomes and early risk factors. Preceding research in this area has often been carried out with small samples, including few females, few studies have investigated the course and risk-factors in European (including Danish) children and the respective studies often suffer from large attrition rates. Thus, there still is a substantial need to expand the knowledge about ADHD across the lifespan especially within a Danish context, including the study of how various risk factors modify the developmental outcomes of these children.

Following these principle considerations, the aim of the present PhD dissertation is to identify how many individuals received a diagnosis of ADHD in Denmark and fulfilled the diagnostic criteria for ADHD, to study the characteristics of these Danish children and adolescents with ADHD, and to estimate how many and what kind of children with ADHD later engage in criminal behaviors. The dissertation is based on

results of five empirical studies, each with specific samples and methods. The characteristics of each study will be described in the following before turning to a summary of the results.

Study I: International studies have shown that an increasing number of children, adolescents and adults have been diagnosed with and treated for ADHD over the last couple of decades [15-22]. Since studies have not established whether a similar trend has taken place in Denmark, nor identified what the mechanisms behind such time-trends could be, the aim of the first study of this thesis was to identify how many children, adolescents, and adults were diagnosed with ADHD during the years 1995 to 2010, and to identify the underlying mechanisms driving this trend. The study was based on data from the Danish Psychiatric Central Research Register (DPCRR) that contains information on diagnoses given in Danish psychiatric departments. In addition, Danish census data from Statistics Denmark was used [23].

Study II: In the Danish child- and adolescent psychiatric departments, children and adolescents are both assessed and treated for ADHD up to the age of 18. International studies have documented that children and adolescents with ADHD often also have co-morbid psychiatric disorders [24] . The purpose of this second study was to assess the prevalence of comorbid psychiatric disorders among children and adolescents diagnosed with ADHD for the first time at age 4-17 years during the years 1995 to 2010, and to establish whether additional factors such as sex, age, or comorbid psychopathology impacted on the prevalence [25]. The study was a cross-sectional study and like Study I, data from the DPCRR formed the basis of the study.

Study III: The aim of the third study was to analyze whether the diagnostic criteria for ADHD according to the International Classification of Disease 10th version (ICD-10) were fulfilled for children and adolescents diagnosed with ADHD aged 4 to 15 years during the years 1995 to 2005. The DPCRR was used to identify children and adolescents diagnosed with ADHD during this time-period and medical records from a randomly sub-selected sample of these children and adolescents were collected from all Danish child and psychiatric departments. The medical records of this sub-sample were systematically assessed in order to determine if diagnostic criteria for ADHD were fulfilled [26].

Study IV: The fourth study of the present thesis was a systematic literature review and meta-analysis that assessed whether ADHD during childhood and adolescence was associated with an increased risk for long-term arrest, conviction or incarceration. This study informed the design of the fifth study. A systematic quality assessment of the included studies analyzed both the strengths and limitations of the

preceding research. Studies were identified by conducting systematic searches in the databases Pubmed, PsycINFO and Embase [27].

Study V: The purpose of the last study of the present dissertation was to follow Danish children and adolescents diagnosed with ADHD longitudinally and identify their risk of conviction and incarceration. The study included data from the ADHD sample from Study III and a randomly selected sample of Danish non-ADHD children and adolescents. The study used data from many Danish registries including the DPCRR, the National Patient Register, the Medical Birth Register, and the Danish Crime Register [28].

In terms of the major results, these five studies found that the number of persons diagnosed with ADHD in the Danish psychiatric hospitals had increased during the years 1995 to 2010. An increase was observed for both sexes and in all age groups, but was especially pronounced among adolescents, adults, and females. Part of the increase in first-time diagnosed ADHD was explained by a more general tendency in the Danish population to be diagnosed with any psychiatric disorders during these years.

Among children and adolescents with ADHD, diagnoses were based on a solid multi-informant approach to psychiatric assessment and the majority of patients fulfilled the diagnostic criteria for ADHD according to ICD-10 criteria. Furthermore, children and adolescents with ADHD often had other comorbid psychiatric disorders and the prevalence of comorbid disorders varied according to the sex and age of the child with some comorbid disorders increasing the risk of having further mental disorders. In addition, children and adolescents with ADHD were identified to more often come from socially disadvantaged families.

The meta-analysis of international studies on crime outcomes showed that children and adolescents with ADHD tended to have a two to three-fold risk for being arrested, convicted, or incarcerated later in life. This observation was confirmed in Study V, but these Danish results also suggested that the risk of conviction associated with ADHD was less pronounced than found in previous studies, as some of the observed risk could be explained in part, by the presence of psychiatric comorbidity and adverse psychosocial backgrounds.

In sum, the present thesis documents that ADHD is a rather common disorder also in Denmark but it was discussed that one may expect that even more individuals will be diagnosed in the years to come, as the frequency of diagnosed ADHD was below international estimates of the frequency of ADHD in the general population. The

studies document, that despite the fact that children and adolescents with ADHD share the same diagnosis, these patients constitute a heterogeneous group with different individual, familiar, and social profiles. Although children and adolescents have an increased risk for long-term convictions, the risk associated with ADHD may be lower than what has been previously assumed. Whereas an important part of the association with crime was explained by ADHD, comorbidity and social adversities in these children and adolescents also explained some of the association. This knowledge should increase the attempts to invest even more strongly into broad psycho-social prevention and treatment programs for at-risk patient groups with ADHD and their families, in order to reduce the risk of long-term crimes.

DANSK RESUME

I Danmark er mistanke om ADHD (*Attention-Deficit/Hyperactivity Disorder*) den hyppigste årsag til, at børn og unge henvises til børne- og ungdomspsykiatrien [1]. Lidelsens kernesymptomer omfatter et mønster af ikke alderssvarende hyperaktivitet, impulsivitet og uopmærksomhed [2]. Studier, der har fulgt børn med ADHD fra barndommen til voksenalderen har bl.a. fundet, at børn med ADHD er i risiko for at få mindre uddannelse, har en øget risiko for kriminalitet, og en større risiko for at udvikle andre psykiatriske lidelser og sågar også har en øget dødelighed sammenlignet med børn og unge uden ADHD [3-9].

Selvom børn og unge med ADHD har en række fællestræk ift. at dele af deres adfærds og funktionsniveau, er børn med ADHD også meget forskellige bl.a. ift., hvilke tillægsvanskeligheder de har, samt ift. deres kognitive, familiære og sociale ressourcer. Disse individuelle forskelle har i udenlandske studier vist sig at være prognostiske [4,6,10-14], dvs. at udsige noget om barnets risikoprofil og senere forløb. Selvom arbejdet på de børne- og ungdomspsykiatriske afdelinger søger at afhjælpe børn og unge med ADHDs vanskeligheder og symptomer her og nu, er målet også, at kunne minimere den indflydelse diagnosen synes at have på barnet og den unges livsforløb. Derfor er det essentielt, at vi ved både, hvad der kendetegner danske børn og unge med ADHD, men også, hvilke karakteristika hos disse børn og deres familier, der kan være vigtige indsatsområder i det forebyggende arbejde.

En større mængde af international forskning har bidraget til en viden om ADHD i et livsforløb, men der mangler forsat meget viden om både forløb og tidlige risikofaktorer. Den allerede udførte forskning på området er præget af relativt små studier, få studier har fokuseret på piger med ADHD, studierne har ofte et stort frafald af studieprobander over tid og meget få studier har undersøgt, forløb og risikofaktorer hos europæiske (herunder danske) børn.

Baseret på disse betragtninger var formålet med indeværende afhandling at identificere, hvor mange personer, der i Danmark er diagnosticeret med ADHD og hvor mange af de diagnosticerede børn og unge, der opfyldte de diagnostiske kriterier for ADHD. Videre sigtede afhandlingen mod at studere, hvad der karakteriserer danske børn og unge med ADHD og endeligt at estimere, hvor mange og hvilke børn, der senere kommer ud i kriminalitet.

Afhandlingen er inddelt i fem studier, med hver deres population og metode. Studiernes karakteristika beskrives i de næste afsnit, hvorefter studiernes resultater opsummeres.

Studie I: Internationale studier har vist, at flere børn, unge og voksne de seneste årtier er blevet diagnosticeret med og behandlet for ADHD [15-22]. Da det ikke har været undersøgt om en lignende udvikling har pågået i Danmark og hvad mekanismerne har kunne være, var formålet med afhandlingens første studie, at identificere, hvor mange børn, unge og voksne, der i årene 1995 til 2010, blev diagnosticeret med ADHD og undersøge, om særlige tendenser underlagde udviklingen i perioden. Studiet anvendte data fra Dansk Psykiatrisk Central Register (DPCR), der indeholder informationer om aktiviteterne på de danske psykiatriske afdelinger, samt census data på den danske befolkning fra Danmarks Statistik [23].

Studie II: På de danske børne- og ungdomspsykiatriske afdelinger udredes og behandles danske børn og unge op til 18. leveår for ADHD. Da internationale studier har peget på, at børn og unge med ADHD ofte har andre komorbide psykiatriske lidelser [24], havde afhandlingens andet studie til formål at undersøge prævalensen af komorbiditet blandt førstegangsdiagnosticerede børn og unge med ADHD i alderen 4 til 17 år, diagnosticeret i 1995 til 2010 og undersøge om prævalensen af psykiatrisk komorbiditet var relateret til faktorer såsom, køn, alder og øvrig psykopatologi [25] . Studiet var et tværsnitsstudie og anvendte lige som Studie I, data fra DPCR.

Studie III: Afhandlingens tredje studie havde til formål at undersøge, om børn og unge diagnosticeret i alderen 4 til 15 år, i perioden 1995 til 2005 med ADHD også opfyldte de diagnostiske kriterier for ADHD jf. Verdenssundhedsorganisationen (WHO) International Classification of Disease 10th version (ICD-10). Formålet med dette studie var at validere ADHD diagnosen hos denne gruppe af patienter, da disse dannede baggrund for afhandlingens femte studie. DPCR blev anvendt til at identificere børn og unge diagnosticeret med ADHD i denne periode. Patientjournaler for et tilfældigt udsnit af denne gruppe blev indhentet fra de danske børne- og ungdomspsykiatriske afdelinger. Informationen fra disse journaler blev systematisk gennemgået og vurderet ift. de diagnostiske kriterier for ADHD i ICD-10.

Studie IV: Afhandlingens fjerde studie var et systematisk litteraturstudie og meta-analyse, der undersøgte, om ADHD i barne- og ungdomsårene var associeret med en øget risiko for senere i livet at blive arresteret, dømt og for at komme i fængsel. Dette studie informerede designet af afhandlingens femte studie ved dels at estimere risikoen associeret med ADHD, dels ved igennem systematisk kvalitetsvurdering af de inkluderede studier, at identificere litteraturens styrker og svagheder. Litteraturen

blev identificeret gennem systematisk søgning i databaserne Pubmed, PsycINFO og Embase [26].

Studie V: Afhandlingens sidste studie havde til formål at følge de børn og unge diagnosticeret med ADHD, hvis diagnoser blev valideret i Studie III, for at undersøge om ADHD også i Danmark er associeret med en øget risiko for at blive dømt og fængslet for kriminalitet senere i livet. Studiet sigtede yderligere mod at identificere, hvilke risikofaktorer i barne- og ungeårene øgede risikoen for kriminalitet senere i livet. Studiet anvendte data fra en lang række danske registre herunder DPCR, Landspatientregisteret, det Medicinske Fødselsregister og Dansk Kriminalregister [28].

Studierne identificerede, at antallet af personer diagnosticeret med ADHD på de danske psykiatriske hospitaler har været stigende i perioden 1995-2010. Stigningen fandt sted hos begge køn og i alle aldersgrupper, men var særligt udpræget i gruppen af unge, voksne og kvinder. En del af stigningen i førstegangsdiagnosticeret ADHD kunne forklares af en mere generel tendens, da der samtidigt blev observeret en stigning i andelen af befolkningen, der er diagnosticeret med mentale forstyrrelser og psykiske lidelser mere overordnet set.

Blandt børn og unge diagnosticeret med ADHD i perioden 1995 til 2005 fandt vi, at diagnoserne ofte var stillet på baggrund af en grundig, multiinformant baseret psykiatrisk udredning og, at flertallet af patienter syntes at opfylde de diagnostiske kriterier for ADHD jf. ICD-10 kriterierne. Studierne identificerede, at børn og unge med ADHD ofte har andre psykiatriske lidelser, og at disse varierer afhængigt af udviklingstrin, køn og ift. hvilke psykiatriske lidelser patienten ellers har. Endvidere blev det dokumenteret, at børn og unge med ADHD udover at have en ophobning af psykiatriske lidelser også oftere kommer fra socialt belastede baggrunde og familier.

Meta-analysen af tidligere publicerede studier viste, at børn og unge med ADHD synes at have en to til tre gange øget risiko for senere i livet at blive arresteret, dømt og fængslet for kriminalitet. Denne tendens blev bekræftet i Studie V, der dog pegede på, at risikoen associeret med ADHD for senere kriminalitet også delvist kunne forklares af faktorer relateret til psykiatrisk komorbiditet og social baggrund.

Opsummerende viser afhandlingen, at ADHD er en diagnose, der også er relativt udbredt i Danmark, selvom det formodentlig må forventes, at flere de kommende år vil blive diagnosticeret, da frekvensen af diagnosticeret ADHD i Danmark ligger under internationale estimater. Studiet tydeliggør, at selvom børn og unge med ADHD har en diagnose tilfælles, udgør disse børn og unge en meget sammensat gruppe med forskelligartede individuelle, familiære og sociale profiler. Studiets

resultater peger på, at selvom børn og unge med ADHD har en øget risiko for senere i livet at komme ud i kriminalitet, så er risikoen forbundet med ADHD mindre end hidtidigt antaget. Studierne peger på, at en del af årsagen til, at børn og unge med ADHD hyppigere udvikler en kriminel løbebane, dels er relateret til at have ADHD, men også er relateret til disse børn og unge har en overhyppighed af adfærdsforstyrrelser og sociale risikofaktorer. Denne viden bør styrke vores opmærksomhed på, og indsats mod, at forebygge kriminalitet ved at tilbyde særlige risikogrupper blandt børn og unge en bred bio-psyko-social indsats og behandling.

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I also want to thank Professor Kristine Jensen de Lopez. In 2012 she supervised my master thesis in psychology and later also my PhD project. She has helped me to remember my background in psychology by constantly pushing me to apply what I learned from other disciplines within the framework of psychology.

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Many thanks to my family and friends, especially to my mother Gitte Mohr Jensen and my father Peder Mohr Jensen. By accepting and encouraging my interest in learning, writing, and talking about my interests throughout my childhood, adolescence, and adulthood you have been shaping my development. Thank you for being there, even though my deep love and enthusiasm for learning at times have left you waiting for a visit or a call. This also applies to my dear and wonderful friends who had the patience for listening to me talking about things they may have found dull but always leaving me with a sense of having their support. May we all enjoy many great years to come in the company of each other.

Finally, I gratefully acknowledge the financial support of this PhD from the Research Unit for Child and Adolescent Psychiatry and the Fund for Clinical Psychiatric Research at Aalborg University Hospital.

Christina Mohr Jensen
Aalborg, February 2016

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I. Jensen, C.M., Steinhausen, H.C. (2015) Time Trends in Incidence rates of Diagnosed Attention-Deficit/Hyperactivity Disorder Across 16 Years in a Nationwide Danish Registry Study, *Journal of Clinical Psychiatry*, 76 (3), e334-41.

II. Jensen, C.M., Steinhausen, H.C. (2015) Comorbid mental disorders in children and adolescents with Attention-Deficit/Hyperactivity Disorder in a large nationwide study, *ADHD- Attention Deficit Hyperactivity Disorder*, 7(1), pp. 27-38.

III. Jensen, C.M., Lauritsen, M.B., Vinkel-Koch, Steinhausen, H.C. (2016) The Validity and Reliability of the Diagnosis of Hyperkinetic Disorders in the Danish Psychiatric Central Research Registry, *European Psychiatry* (In press).

IV. Jensen, C.M., Steinhausen, H.C. (2015) A systematic review and meta-analysis of Arrests, Convictions, and Incarcerations at Long-term Follow-up of Individuals with Childhood Attention-Deficit Hyperactivity Disorder (Submitted).

V. Jensen, C.M., Bisgaard, C., Steinhausen, H.C. (2016) Attention-Deficit Hyperactivity Disorder and the Risk of Crime in Young Adulthood in a Danish Nationwide Follow-up Study (Submitted).

Due to copy-right conditions the articles are not published in the dissertation and only available in print for the PhD committee.

CHAPTER 1. BACKGROUND

In Denmark suspicion of Attention-Deficit Hyperactivity Disorder (ADHD) is the most frequent reason to refer children and adolescents to the child- and adolescents psychiatric hospitals [1]. Therefore, it is also critical, that we obtain knowledge about ADHD in Danish children and adolescents. The present dissertation is situated in one of the most active clinical and research domains of child and adolescent psychiatry and psychology, namely, ADHD. The specific foci of the dissertation are on time trends in incidence rates of diagnosed ADHD, validity of the diagnosis, coexisting mental disorders, and crime as a major long-term consequence of this disorder originating early in life.

Throughout this dissertation, the term ADHD will be used synonymously with Hyperkinetic disorders (HD), as the term ADHD has been used among professionals and nonprofessionals both nationally and internationally to characterize this phenotype. Whenever referring specifically to differences between HD and ADHD, the term HD will however be used.

1.1. THE DEFINITION OF ADHD

The classification of all mental disorders is based on categorizing various psychological and behavioral phenomena existing along a continuum from normal to abnormal. If many of a given set of behaviors and psychological traits or experiences accumulate in an individual this can be associated with difficulties sustaining and maintaining functioning in the society in which this individual is embedded. The observable characteristics form what is named a phenotype – a word stemming from the Greek words *phainein* and *typos* meaning "to show" and "type". Thus, the classification of mental disorders is different from the classification of many somatic conditions since the distinction of the normal and the abnormal is not clear cut, and mental disorders are not classified based on their etiology but are phenomenological in nature.

Internationally two diagnostic systems are currently in use, namely, the International Classification of Diseases 10th edition (ICD-10) [2] and the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5)[29]. Both systems include a phenotype characterized by various cognitive problems including inattentiveness and forgetfulness, excessive hyperactivity and impulsivity. In the ICD-10 this phenotype

is called HD whereas the DSM-5 names it ADHD. In both ICD-10 and DSM-5, children and adolescents have to present with a minimum of six symptoms of inattention. Whereas the ICD-10 have specific cut-off criteria for hyperactivity (at least three symptoms) and impulsivity (at least one symptom) separately, the DSM-5 collapses symptoms of hyperactivity and impulsivity and requires six symptoms in this domain.

Despite great overlap in the diagnostic criteria for HD and ADHD there are various differences, including whether clinicians should rate symptoms on three (ICD-10) or two domains (DSM-5) as described above. Also, contrary to the ICD-10, in the DSM-5 clinicians have to specify whether the person has a primarily combined, inattentive or hyperactive-impulsive presentation of symptoms [29].

Also the criteria for the age of onset of when these symptoms have to become apparent differ between ICD-10 and DSM-5. According to the ICD-10, the problems must become apparent before the age of seven, while the more recent DSM-5 has expanded the age of onset criterion to the age of 12. Unlike the definitions in ICD-10, the symptom cutoff is lowered in the DSM-5 for individuals above the age of 16 years to accommodate the diagnostic criteria to the developmental changes in symptom presentation during the lifespan [30] . In both classifications, it is a requirement that symptoms have been present for a minimum of six months and that they require symptoms to be present and contribute to substantial impairment in at least two developmentally important settings, such as school and family life in children and work and romantic relationships in adults.

ADHD, like other mental disorders, are classified based on symptoms. Although on a group level individuals with ADHD can be distinguished on neuropsychological, brain anatomical, and functional measures from normal controls, individuals with ADHD represent a heterogeneous group and no single abnormality or set of abnormalities can be used to distinguish ADHD from non-ADHD with high enough sensitivity or specificity [31].

1.2. THE HISTORY OF THE CONCEPT OF ADHD

As with most psychiatric entities, the construct of ADHD has changed over time. The first clinical descriptions reminiscent of our current conceptualization of this phenotype came from the Scottish physician Sir Alexander Crichton in 1798 who in his book "*Attention and its Diseases*" described the importance of attentional functions and the critical outcomes of a disturbed capacity to attend [32]:

> *"When born with a person [the incapacity of attending] it becomes evident at a very early period of life, and has a very bad effect, inasmuch as it renders him incapable of attending with constancy to any one object of education."*
>
> *"In this disease of attention, if it can with propriety be called so, every impression seems to agitate the person, and gives him or her an unnatural degree of mental restlessness. People walking up and down the room, a slight noise in the same, the moving a table, the shutting a door suddenly, a slight excess of heat or of cold, too much light, or too little light, all destroy constant attention in such patients, inasmuch as it is easily excited by every impression. ….When people are affected in this manner, which they very frequently are, they have a particular name for the state of their nerves, which is expressive enough of their feelings. They say they have the fidgets".*
>
> *Alexander Crichton, 1798*

Later in 1902 the British pediatrician George Frederic Still took the first steps towards describing ADHD as a mental disorder. In his lectures he described what he called *"…an abnormal defect of moral control in children"* [33]. Moral control was described as dependent on three factors: cognitive relation to the environment, moral consciousness and volition. He noticed that the *defect of moral control* was often observed in children with intellectual disabilities but he also described 20 cases of children with a morbid manifestation of the *defect of moral control* without intellectual impairment or physical disease such as meningitis or cerebral palsy. These cases were characterized by a drive towards immediate gratification of themselves, without regarding the needs of others or the more *"…remote good of self"* [33].

In line with the work by Alexander Crichton, he described children with impairing attention problems in the following way:

> *"…the case of a boy with moral defect who would repeat the process of saying 'Good-night' several times before he was aware that he had done so; the same boy would often put his boot on the wrong foot apparently without noticing it. Another boy, aged six years, with marked moral defect was unable to keep his attention even to a game for more than a very short time, and, as might be expected, the failure of attention was very noticeable at school, with the result that in some cases the child was backward in school attainments, although in manner and ordinary conversation he appeared as bright and intelligent as any child could be."*
>
> *George Frederic Still, 1902*

Later during a global epidemic of encephalitis lethargica that took place from 1917 to 1928 there was an increasing interest in the organic cause of childhood inattention, hyperactivity, and impulsivity known as *Postencephalitic behavior disorder*. In 1932, the German physicians Franz Kramer and Hans Pollow described the condition of *"Hyperkinetic disease of infancy"* marked by motor restlessness, difficulties staying on task, and impaired sustained attention. This condition was described with an onset before the age of four and as an organic disorder resulting from severe fevers or epileptic convulsions [34]. These observations, in combination with the identification of the therapeutic effects of Benzedrine on the symptoms by Charles Bradley in 1937, gave nurture to the development of the concept of *Minimal Brain Damage*, which Rosenfeld and Bradley in 1948 described as [35]:

> *"…a fairly uniform overt behavior pattern in maladjusted children who have experienced asphyxiant illness in infancy. Six cardinal behavior characteristics make up this syndrome and may be listed as follows: 1. Unpredictable variability in mood; 2. Hypermotility; 3. Impulsiveness; 4. Short attention span; 5. Fluctuant ability to recall material previously learned; and 6. Conspicuous difficulty with arithmetic in school.*
>
> *Rosenfeld and Bradley, 1948*

Later on in the 1960's criticism began to emerge towards the practice of inferring brain damage in children with a lack of evidence demonstrating actual neurological damage, and so the condition was renamed Minimal Brain Dysfunction (MBD)[35]. As

a consequence, the Oxford International Study Group of Child Neurology re-conceptualized the hyperkinetic symptoms in terms of functional rather than structural abnormalities of the brains of the affected children [35].

However, as strong correlations between individuals with either brain damage or dysfunction and the observed symptoms of hyperactivity were not evident; there was a move towards defining the concept on phenomenological rather than aetiological grounds. This development was reflected with the introduction of DSM in 1968 by re-naming the concept *"Hyperkinetic Reaction of Childhood"* in DSM-II. In this first diagnostic formulation, the symptoms of hyperactivity were very much emphasized as core symptoms but the presence of distractibility and short attention span were also mentioned [36]. In parallel, the ICD-8, published in 1965, also included a description of *"Hyperkinetic reaction of childhood"* emphasizing hyperactivity as the core feature [37]. The ICD-8 system was in use in Denmark until the introduction of the later ICD-10 in 1995.

Later, in the 1980's there was a shift towards a stronger emphasis of the attention problems seen in hyperactive children. The Canadian Psychological Association argued that symptoms of inattention and impulse control were the core-features, showing the best response to stimulant treatment, which led to the disorder being relabeled *"Attention Deficit Disorder with or without Hyperactivity"* in DSM-III [38]. According to DSM-III criteria, hyperactivity was now no longer a critical symptom for making the diagnosis but could be either present or absent. This reconceptualization differed from the approach in the ICD-9 classification, which continued to define hyperactivity as a key feature of the disorder. The ICD-9 was never introduced and used in Denmark.

The introduction of the DSM-III paved the way for the current diagnostic classification by defining cut-off scores for symptoms and criteria for age of onset and duration of symptoms [39]. However, the distinction of ADD with or without hyperactivity was soon abandoned in the revised the DSM-III-R, due to the lack of an empirical basis for the two subtypes, and the disorder was re-named *"Attention deficit-Hyperactivity Disorder"*. Individuals presenting only with symptoms of inattention were now assigned to the category of *"Undifferentiated ADD"* [40]. Based on a more solid empirical ground, DSM-IV in 1994 reintroduced the subtyping of ADHD after a large field trial had identified two latent classes of symptoms, namely, inattention and hyperactivity-impulsivity [41]. This led the DSM-IV to now distinguish between children with primarily inattention, primarily hyperactive-impulsive behaviour or a combined subtype [42].

The ICD-10, which was also published in 1994 had an almost identical list of symptoms to the DSM-IV but did not leave room for subtyping children with *"Hyperkinetic Disorders"*. Currently, the ICD-10 criteria are still in use [2], while the DSM-IV in 2014 was substituted by the DSM-5 [29]. In this most recent classification, the subtyping of ADHD was abandoned again due to the demonstration, that subtypes have limited validity [43], and clinicians were instead asked to specify the primary symptom presentation. In addition, the age of onset criterion was changed from age seven to age 12 and the cut-off symptom criteria were lowered for individuals above the age of 16. This change was initiated to make the diagnostic criteria more sensitive to the developmental changes in symptom presentation of ADHD later in life [30].

1.3. IMPACT OF DIAGNOSTIC CLASSIFICATIONS ON INDIVIDUALS IDENTIFIED WITH ADHD

1.3.1. FROM DSM-II TO DSM-5

Changing criteria for a disorder results in changing populations defined by this disorder. Only a few studies systematically evaluated these consequences in terms of case-identification. No studies have looked into the consequences of changing the definition from MBD to the DSM-II criteria for Hyperkinetic reaction of childhood. One study identified that out of 110 cases diagnosed according to DSM-II criteria, only 61 (55.4%) also fulfilled criteria for DSM-III ADD with or without hyperactivity [44]. This finding suggests a relatively poor overlap of DSM-II and DSM-III criteria. Furthermore, there was an increase equal to 1.8% in prevalence of cases using DSM-III compared to DSM-II criteria. Out of the "new" cases, 52% were diagnosed with ADD without hyperactivity suggesting that the DSM-III was more sensitive to individuals with primarily symptoms of inattention [44].

When the DSM-III was replaced by the DSM-III-R, studies suggested a good overlap (90-95%) between the criteria in these two versions. In addition, with the revised system (DSM-III-R) an increased number of new cases were identified (7.1-14.4% increase in case-identification) [45,46]. It was assumed that this increase was related to a higher sensitivity to individuals with primarily hyperactive-impulsive symptoms and also to those with primarily symptoms of inattention [45,46].
A strong overlap in case identification amounting to 93-98% was also present when the DSM-III-R criteria were replaced by the DSM-IV criteria [41,47,48]. The use of DSM-IV resulted in a 7-15% increase in case-definitions which was primarily related to

even higher sensitivity to individuals with the primarily inattentive subtype, to females and to adolescents with ADHD [41]. In addition, the DSM-IV has been described as being more sensitive to less complex cases of ADHD. A comparison of cases identified by DSM-III-R criteria and DSM-IV criteria revealed that the new cases identified by DSM-IV criteria had less comorbidity of psychiatric disorders, such as a lower prevalence of bipolar disorder and conduct disorders [49]. Further comparisons of the DSM-III and DSM-IV criteria showed that the change in diagnostic criteria identified 6.5% more cases with ADHD [49].

Consequences in terms of differences in case-identification have also been studied with the recent shift from DSM-IV to DSM-5. In particular, the change in the age of onset criteria from age seven in DSM-IV to age 12 years in the DSM-5 has been the focus of studies as the ADHD diagnosis was not tested in adult populations during the DSM-5 field trials [50]. Based on findings from a birth-cohort, it was estimated that the change in onset criteria would have minimal impact on prevalence estimates among seven to 12 year olds, as only 0.1% of newly identified children and adolescents with ADHD reported an onset between the ages of seven to 12 years[51]. However, in adolescents it was established that DSM-IV identified only 7.4% of adolescents with ADHD, whereas DSM-5 identified a total of 10.8% [52]. This study also showed that the clinical features and functional impairment of those with an onset between age seven and 12 years was non-significantly different from those with an onset before age seven.

A recent Chinese study on self-referred adult individuals found that 22% of individuals identified with ADHD had an onset between age seven and 12 years. This study identified a decreased quality of life and functional impairment which was similar for those with childhood versus late-onset ADHD [53]. Finally, using data from the Brazil Pelotas Birth Cohort, DSM-5 criteria identified 27% more adults with ADHD at a prevalence of 3.55% using DSM-5 criteria versus 2.8% when using DSM-IV criteria. This study also supported the validity of lowering the symptom cut-off criteria for individuals above the age of 16 to adequately identify individuals with substantial impairment [54].

In summary, on the one hand these studies suggest that by each new revision of the diagnostic criteria for ADHD the identified population had become larger and more heterogeneous, while on the other hand some cases identified by the preceding system were not classified as having ADHD in the next. It is likely that the early identifications of ADHD by for example, DSM-II criteria contained a rather mixed group of individuals with ADHD and other behavioral disorders, whereas the newer systems including the most recent DSM-5 criteria are more sensitive to individuals

primarily affected by symptoms of inattention, to less complex cases of ADHD, to females, to adolescents, and to adults with ADHD. Despite this broadening of the identified patient-group there is sufficient evidence that the diagnostic criteria are sensitive and specific for individuals with impairment.

1.3.2. COMPARISON OF DSM-IV AND ICD-10

So far, studies have not assessed the overlap and differences associated with assessing populations using ICD-10 criteria versus DSM-5 criteria. Therefore, the differences in case-definitions can only be described for ICD-10/DSM-IV. In The Multimodal Treatment Study of Children with ADHD (MTA), a randomized controlled trial of children with ADHD assessing the efficacy of various interventions, 579 children fulfilling DSM-IV criteria for ADHD were assessed using ICD-10 criteria. Only 25% of children (145 out of 579) fulfilled criteria for HD [55].

Similar findings have been identified in a study assessing the predictive validity of HD compared to DSM-IV defined ADHD over a six year period of follow-up. In N=95 included children aged 4-6 years all meeting DSM-IV - criteria for ADHD, only 26% fulfilled criteria for HD [56]. These findings have been used to argue that ICD-10 might overlook children with substantial impairment and children at high risk of a negative social, educational, and mental health well-being[56].

1.4. PREVALENCE OF ADHD

Due to the historical changes in the concept of ADHD over the last 60 years including the differences in classification by either ICD or DSM, it is difficult to arrive at reliable estimates of the frequency of ADHD in the population. The most comprehensive meta-analysis estimating the point prevalence of ADHD published to date included studies that used probalistic sampling strategies in the general population under the age of 18, and identified the prevalence of ADHD using the criteria provided by either DSM-III, or DSM-III-R, DSM-IV, ICD-9 or ICD-10 [57]. This meta-analysis included 102 studies and arrived at a pooled ADHD point prevalence of 5.29% (95% CI=5.01-5.56). The estimated prevalence was higher in males than in females (2:1 ratio) and the prevalence was higher in children compared to adolescents. The study did not identify differences in prevalence estimates between North American and Europe [57].

For many years it was assumed that ADHD was a childhood disorder. However, using prospective longitudinal research designs it has been established that ADHD persists

into adolescence and adulthood [30]. It was estimated that 15% of childhood ADHD cases would continue to meet the full DSM-IV diagnostic criteria for ADHD at age 25, while 65% would fulfill diagnostic criteria for ADHD in partial remission [58]. Given this rate of persistence, it was projected that 1.2% of the adult population would meet the full set of DSM-IV criteria for ADHD in adulthood and 3.2% would fulfill the criteria for ADHD in partial remission [58]. Actually, according to the World Health Organization World Mental Health Survey Initiative the average prevalence of ADHD in adults age 18-44 is 3.4% [59]. Thus, ADHD is a relatively common psychiatric disorder in the population. There are no large-scale population based studies in Denmark that have tested whether the prevalence of ADHD is in accordance with the findings from the international literature, but there is no reason to suspect that the prevalence should be different in Denmark.

Despite lacking Danish ADHD prevalence studies, it has become increasingly clear in Denmark, as well as in other countries, that an increasing proportion of individuals are both diagnosed with and treated for ADHD [15-22]. Danish studies provide evidence that there are regional differences in the incidence rates of treated and diagnosed ADHD [19,60,61], but it is not clear in which subgroups in the population these changes have taken place. It is important to identify the number of Danish individuals diagnosed with ADHD and to analyse the mechanisms driving the observed increase in the number of newly diagnosed individuals to find out whether the observed increase is reasonable. In addition, apart from establishing how many individuals are diagnosed, it is critical to ascertain whether the diagnosed children and adolescents actually fulfil the criteria for ADHD. This issue is highly relevant as a challenge of the widely held opinion in the public, the media, and among some professionals that ADHD is over-diagnosed.

1.5. ADHD AND PSYCHIATRIC CO-MORBIDITIES

As described above in section 1.1, patients with ADHD do not constitute a homogenous group of individuals, in terms of their clinical characteristics. Comorbidity adds to this heterogeneity and, in fact, multiple studies have provided evidence that ADHD often co-occurs with other mental disorders [31,62,63]. It is difficult to arrive at good estimates of psychiatric comorbidities in ADHD during childhood, adolescence and adulthood, as sample definitions can impact on findings. First of all, clinical samples or treated samples of children with ADHD tend to have a higher frequency of comorbid psychiatric disorders when compared to affected individuals in the community [64] because more severe, complex, and chronic cases are likely to be referred to psychiatric services. This selection bias, which is known as “the clinicians illusion” [65], in turn tends to inflate findings of other comorbid disorders in

clinical samples, as the probability of having one disorder, e.g. depression significantly increases the risk of other comorbid conditions such as anxiety disorders independently of the ADHD status. This phenomenon is known as Berkson`s bias [66].

Secondly, by applying various sorts of in- and exclusion criteria in defining samples of ADHD also the frequency of other psychiatric conditions in the sample will be affected. For instance, if one would systematically exclude patients with ADHD and co-occurring depression, the prevalence estimates of the co-occurrence with anxiety disorders would be affected, as these two disorders are known to co-exist frequently.. Whereas internalizing disorders are not often used as exclusion criteria in studies, clinical trials and prospective follow-up studies have often systematically excluded individuals with autism spectrum disorder (ASD) and intellectual disability (ID)[67-69].

Thirdly, the prevalence of mental disorders co-morbid to ADHD also varies according to the temporal definitions of co-existence, for example, whether prevalence is estimated during the last six months, during the last year or defined as life-time prevalence. Fourthly and finally, because the development of mental disorders is sensitive to developmental changes, so is the pattern of psychiatric comorbidity seen in patients with ADHD [24]. While disorders such as ASD and intellectual disability have their onset early in life, other disorders such as depression and substance use disorders most frequently have their onset in adolescence and adulthood [24]. Thus, when inspecting the literature on ADHD and co-morbidity one must carefully take into consideration where, when, and how the sample was defined and assessed.

Taking these methodological and developmental considerations into account, both community and clinical samples found that the most frequent psychiatric conditions comorbid with ADHD are oppositional defiant disorder (ODD) and conduct disorder (CD) in childhood and adolescence. In the MTA study assessing the efficacy of various treatments on ADHD in N=579 children and adolescents with ADHD in the age-range 7 to 9.9 years, 39.9% fulfilled diagnostic criteria for ODD and 14.3% fulfilled criteria for the more severe CD[70]. This finding was corroborated by multiple studies with prevalence rates of ODD/CD in the 4 - 60% range [64,71-79].

The second most frequently observed psychiatric condition in the MTA study at baseline was anxiety disorders affecting 33.5% of the sample [70]. These findings are in line with conclusions from reviews finding that 10 to 35% of children fulfil diagnostic criteria for anxiety disorders [24,62,63]. Affective disorders such as depression were relatively rare in the MTA sample (3.8%) [70] and have been found to co-exist with ADHD to a greater extent later in life [62,63] following the common clinical

observation that depression most frequently develops in adolescence and adulthood [80].

In the MTA, tic disorders were relatively frequently observed with 10.9% being affected [70]. However, as the MTA included a clinical trial with methylphenidate [70], cases with severe tics or Tourette were excluded and thus, the prevalence of children with ADHD and tic disorders most likely was higher. Various other mental disorders like e.g. ID were not reported in the MTA study and moderate to severe obsessive compulsive disorder (OCD) served as exclusion criteria [70].

Other studies have found that elimination disorders co-exist with ADHD in 22-32% of children [24,81,82]. Specific disorders of learning, motor and language development have also frequently been observed in ADHD samples with findings in the wide range of 10 to 42 % [62,75,76,83-86]. The co-occurrence of ADHD with ID and ASD has been studied less frequently although children with these conditions are seen quite frequently in the clinic. Studies that have looked into the prevalence of ID find that between four to 13% of children with ADHD are affected [74,75,87,88] and the prevalence of comorbid ASD has been found in 4-10 % of samples [76,89]. Later in development, there is evidence to suggest that ADHD often co-occurs with personality disorders and substance use disorders [24,90-92].

In summary, the study of the co-occurrence of comorbid disorders in children and adolescents with ADHD is complex and findings are depending on when and in which samples comorbidity is assessed, and which criteria and definitions are used to estimate the prevalence. However, it is clear that many psychiatric conditions such as learning disabilities, ODD/CD, ID, ASD are more frequent in children and adolescents with ADHD than in normal controls [24]. The large overlap of these diagnostic entities confer an excess of risk on affected individuals for various adverse developmental outcomes which are not nessecarily the result of ADHD alone. There is a need to study a broad range of clinical conditions potentially co-occuring with ADHD using large representative samples and studies that look at psychiatric comorbidity in a developmentally sensitive way. There is also a need to try to deliniate in which subgroups of patients which comorbid disorders tend to aggregate, as these may represent meaningful subgroups of patients with different treatment needs and different long-term risks and outcomes.

1.6. COURSE OF ADHD ACROSS THE LIFESPAN

Various prospective case-control studies have been carried out over the last 50 years that have helped to guide our understanding of how children and adolescents with

ADHD develop and function in the long term. An overview of selected long-term follow-up studies of children and adolescents with ADHD is presented in Table 1 and Table 2. Most of these studies have been carried out in the United States of America (US), and these studies have primarily followed males with ADHD. A large majority of studies recruited clinical samples of children and adolescents with ADHD only and most studies systematically excluded individuals with an IQ below 80-85, individuals with neurological conditions such as cerebral palsy or epilepsy, and children with ASD. The majority of studies used DSM-II-, DSM-III-, and DSM-III-R-criteria to include individuals with ADHD.

Only one study from Denmark has performed a long-term follow-up study of a well-defined cohort of children and adolescents with problems equivalent to ADHD [6]. The sample consisted of 208 children and adolescents referred to a psychiatric clinic in Aarhus during the years 1969 to 1989, who were treated with methylphenidate or dexamphetamine. Material from the patient records of these children and adolescents were later re-assessed and it was found that 81% fulfilled full or subthreshold DSM-IV/ICD-10-criteria for ADHD [69].

This overview clearly shows that longitudinal follow-up studies of children and adolescents with ADHD are lacking representativeness to the children and adolescents seen in the clinics by for example including few females, and often excluding individuals with relatively common psychiatric comorbidities such as ID and ASD. In addition, as many studies were initiated when DSM-II-, DSM-III- and DSM-III-R-criteria were in use and based on the descriptions in section 1.3.1, it is uncertain to what extent the findings generalize from these historical cohorts to children and adolescents diagnosed with ADHD nowadays.

Studying the long-term outcome of children and adolescents with ADHD is rather complex, as a range of factors associated with long-term negative outcomes accumulate in these samples compared to control children. First of all, ADHD often co-exist with other mental disorders, as described in the previous section. Each of these psychiatric disorders conveys its own risk on long-term development. In addition, children and adolescents with ADHD are more likely to come from low SES strata [93] and have parents with psychiatric disorders including ADHD, personality disorders and affective disorders [67], each of which are risk-factors for adverse psychosocial outcomes.

Table 1 Selected follow-up studies of children and adolescents with ADHD

Authors	Country	Definition of ADHD	N at baseline	Percent males
Barkley et al. (1990) [12]	Milwaukee, USA	DSM-III-like criteria	ADHD n=158 Controls n=81	90.3%
Biederman et al. (1992) [67]	Massachusetts, USA	DSM-III-R	ADHD n=140 Controls n=120	100%
Biederman et al. (1999) [94]	Massachusetts, USA	DSM-III-R	ADHD n=140 Controls n=122	0%
Dalsgaard et al. (2001) [69]	Aarhus, Denmark	Inattentive/ hyperactive treated with stimulants	ADHD n=208 Danish population	87%
Hinshaw et al. (2012) [68]	San Fransisco, USA	DSM-IV	ADHD n=140 Controls n=88	0%
Mannuzza et al. (1989) [11]	New York, USA	DSM-II	ADHD n=207 Controls n=100	100%
Satterfield et al.(1982) [95]	Los Angeles, USA	Hyperactivity, impulsivity, poor attention span	ADHD n=204 Controls n=75	100%
Weiss et al. (1984) [13]	Montreal, Canada	Restlessness poor attention span	ADHD n=104 Controls n=45	92%

DSM: Diagnostic and Statistical Manual of Mental Disorders

Table 2 In and exclusion criteria for cases and controls in selected long-term follow-up studies of children and adolescents with ADHD

Authors	Inclusion ADHD	Inclusion controls
Barkley et al. (1990) [12]	Hospital referred children, IQ>80, no gross motor or sensory abnormalities	Snowball recruitment method among cases, no history of mental illness or parental report of behavioral problems
Biederman et al. (1992) [67]	Hospital referred children, IQ>80, no gross motor or sensory abnormalities, psychosis, autism, families from very low SES strata excluded	Recruited from local outpatient pediatric clinics
Biederman et al. (1999) [94]	Hospital referred children, IQ>80, no gross motor or sensory abnormalities, psychosis, autism, families from very low SES strata excluded	Recruited from local outpatient pediatric clinics
Dalsgaard et al. (2001) [69]	Hospital referred children, no pervasive developmental disorders	The Danish general population used as control group
Hinshaw et al. (2012) [68]	Recruited from schools, hospitals and mental health settings. Exclusion criteria; intellectual disability, pervasive developmental disorder, psychosis and overt neurological disorder.	Recruited from same setting as ADHD sample but were free of ADHD and fulfilled same exclusion criteria as ADHD sample
Mannuzza et al. (1989) [11]	Hospital referred children, no aggressive or serious conduct problems, IQ>85, no psychosis or neurological disorder	Recruited from non-psychiatric departments seen for minor ailments (e.g. influenza) and among non-affected siblings of ADHD sample
Satterfield et al.(1982) [95]	Hospital referred children, IQ>80, no sensory abnormalities, no psychosis, attending school	Recruited from public schools and matched to ADHD sample on IQ, age and sex. No history of psychiatric problems.
Weiss et al. (1984) [13]	Hospital referred children, IQ>85, no psychosis epilepsy or cerebral palsy	Recruited from local schools via advertisement. No behavioral problems, matched to ADHD sample on IQ, SES, sex and age

IQ: Intelligence quotient; SES: socio-economic status

1.6.1. PSYCHIATRIC OUTCOMES

Findings from long-term follow-up studies of children and adolescents with ADHD have shown that for many individuals, ADHD has a sizeable long-term impact on developmental outcomes. As described earlier, a meta-analysis identified that an estimated 15% of children will continue to fulfill diagnostic criteria at age 25, but up to 65% will fulfill diagnostic criteria for ADHD in partial remission and continue to have functional impairment [58,96]. Apart from this finding, long-term follow-up studies have also documented an increased risk of developing other psychiatric disorders later in life. At the 16 year follow-up point, the Massachusetts study sample had a mean age of 27.1 (Standard deviation (SD) 3.3) years and the life-time prevalence of mood disorders was approximately 60% in the ADHD sample compared to 20% in control subjects. This study found that individuals with ADHD had an increased risk of anxiety disorders including agoraphobia, social phobia, OCD and specific phobias (65 vs. 40%), antisocial disorders including CD/ODD and antisocial personality disorders (APD) (80 vs. 30%) [3]. These findings were corroborated by other long-term follow-up studies [5,6,97].

In addition to the findings from the Massachusetts sample, the New York study has found an elevated risk of children and adolescents with ADHD for long-term substance use problems (56 vs. 38%) when estimating the life-time prevalence of mental disorders at age 44 years [5]. A significant increased risk of long-term substance use disorders [6,14,98], self-harm [68], and various kinds of personality disorders has been observed in various samples [92,97]. Early predictors of adverse psychiatric outcomes have been found to be related specifically to symptoms of CD early in life, which increase the likelihood for later APD, and substance use disorders [4,6,10-13].

1.6.2. EDUCATIONAL AND OCCOPATIONAL OUTCOMES

Among the various developmental outcomes, the core symptoms of ADHD also have an impact on the individual`s capacity to learn and take part in the educational system. Long-term outcome studies have shown that children and adolescents in adulthood are less likely to graduate from high school, display an increased risk of repeating grades and getting detentions, or are expelled from schools and in general, receive less years of education than healthy controls [3,8,12,68,99-101]. In the Milwaukee studies following up participants until age 19-25 years, a total of 42% of the ADHD sample compared to 13% of the controls had retained a grade, 60% vs. 18% had been suspended during high school, only 68% vs. 100% had graduated high-school, and only 15% vs. 76% were still studying at the follow-up assessment [102]. In particular, the number of symptoms of inattention but also symptoms of hyperactivity [103,104],

comorbidity with CD and ODD [8,102,105,106], childhood IQ [100] and family adversity [100] were predictors of academic achievement.

In addition to this, long-term outcome studies have shown poorer work-life outcomes for adults who had a diagnosis of ADHD in childhood, which has consequences for economic independence. These studies demonstrate that adults with a childhood diagnosis of ADHD have higher levels of unemployment, are more likely to have been laid off or to change jobs multiple times and have lower occupational ranks, even after controlling for the impact of other psychiatric disorders comorbid to ADHD [3-5,102]. Again, in the Milwaukee studies at the follow-up assessment at age 19 to 25 years, a total of 55% of the individuals with childhood ADHD had experienced being fired from a job compared to 23% of the control sample, less had a savings account (52 vs. 70%), and more had difficulty saving to pay bills (44 vs. 30%). Furthermore, the ADHD sample had changed their occupation more often than controls (Mean= 2.6, SD=2.4 vs. Mean=1.3, SD=1.3), and were also fired from their jobs significantly more often. Though not significantly distinguishable at this follow-up, the ADHD sample had more credit card debt (845 $ vs. 469$), and they owed significantly more money to other people (Mean=949$, SD=1210$ vs. Mean=412$, SD=502$).

This study found that the inability to maintain employment was significantly associated with employer- rated symptoms of ADHD and self-reported symptoms of current ODD. On the contrary, current IQ and severity of childhood ADHD symptom severity were not predictive of this outcome. In the same study, severity of childhood hyperactivity and employer-reported symptoms of ADHD were significantly associated with current job performance [102]. In summary, the consequences of these educational and occupational outcomes resulted in a lower SES of adults with childhood ADHD compared to controls [5]. Cross-sectional studies of adults support these findings [107,108].

1.6.3. ANTISOCIAL OUTCOMES

As children and adolescents with ADHD have been shown to experience a higher prevalence of both ODD/CD, APD, and substance use problems, an increased risk of antisocial involvement has also been documented in long-term outcome studies. Substance use and possession is by itself illegal and many of the symptoms in both ICD and DSM for ODD/CD and APD cover behaviors that are directly violations of legislations. For example, symptoms like *“has stolen”, “has been physically cruel to people or animals”, “has used a weapon that can cause serious physical harm to*

others" or *"has forced someone into sexual activity"* are among the definitions of these disorders [2,29].

The overrepresentation of individuals with ADHD in crime statistics has been firmly established in a recent meta-analysis of prevalence studies of ADHD in incarcerated populations, estimating that 30.1% of incarcerated youths and 26.2% of incarcerated adults fulfilled diagnostic criteria for ADHD [109]. This is equivalent to a five and ten fold increase compared to estimations from the general population [109]. The fifth paper of this dissertation represents a systematic review and meta-analysis of the long-term risk of antisocial involvement measured in official arrest records, and thus results from this type of studies will be covered later in the dissertation (section 3.4). However, a brief overview of the findings from the Milwaukee study will be presented below, because it provides an insight into the antisocial involvement that had been self-reported by adults. This documentation is reasonable, because the review focus is on data from official crime records which typically only detect a proportion of all committed criminal acts, since not all antisocial acts come to the attention of the law enforcement [110]. On the other hand, self-reports on antisocial engagement are likely to be influenced by a bias due to underreporting or exaggerations [110].

At the follow-up assessment at age 20 to 21 years, when comparing the ADHD sample vs. controls, the Milwaukee study found significant differences on most self-reported items of antisocial behaviors, except for robbery/mugging (4 vs. 0%), forcing someone into sex (1 vs. 0%), sex with a prostitute (2 vs. 0%), illegal drug possession (52 vs.42%), and illegal drug sale (24 vs. 20%). The ADHD participants reported higher frequencies across all the various antisocial acts compared to control participants. Adults with childhood ADHD self-reported that to a larger extent they had stolen property (85 vs. 64%), had stolen money (50 vs. 36%), had broken into homes (20 vs. 8%), had conducted themselves disorderly (69 vs. 53%), had been in fist-fights (74 vs. 52%), had assaulted someone with a weapon (22 vs. 7%), had set serious fires (15 vs. 5%), and had carried a concealed weapon (38 vs. 11%). A higher number had been arrested at least once (54 vs. 37%), more than twice (39 vs.12%) and more than three times (27 vs. 11%) [14]. Despite the antisocial nature of some of these behaviours, some seem to be relatively frequent even among typically developing individuals, such as having stolen property or money. This study found that the presence of ADHD symptoms in childhood, adolescence and adulthood, adolescent symptoms of conduct disorder, and adolescent drug use predicted engagement in antisocial activities [14].

In addition, the Los Angeles studies established the finding that adolescent crime history predicted adult crime engagement. Younger age at first crime significantly increased the risk of repeated offending and parent and teacher reported behaviour problems, such as lying or taking money from family members in childhood predicted juvenile and adult delinquency, along with lower IQ and lower SES [111,112]. The significance of early emerging CD problems and ODD behaviors and low SES as predictors for antisocial involvement has also been identified in other studies [113,114]. However, evidence from the New York studies suggest that childhood behavior problems are not the only predictors of adult criminality, as this study excluded children with childhood CD [9].

It is important to note, however, that various factors apart from psychiatric comorbidity, are likely operant as early risk-factors for later antisocial involvement independent of ADHD exposure. According to a major review of the literature published by the Office of Juvenile Justice and Delinquency Prevention from the US Department of Justice (2004), these risk-factors operate on various levels ranging from individual to familial over societal risk-factors and work in a multiplicative fashion to increase the individual`s probability of becoming involved in antisocial activities (See Figure 1) [115].

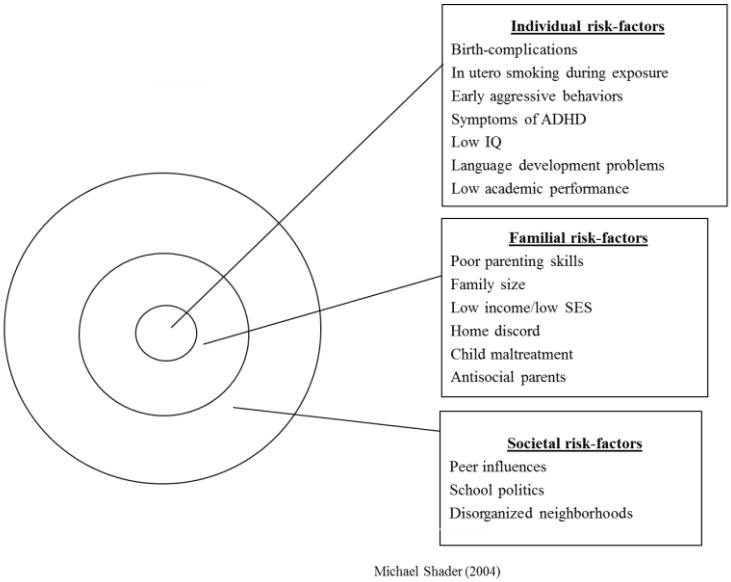

Figure 1 Risk factors for long-term criminality

The literature described above clearly indicates that many of these factors are more frequently found in children with ADHD and the families of children with ADHD, such as an increased risk of lower educational attainment, higher risk of low IQ, CD problems, lower family SES, and school expulsions. However, it may be important to distinguish between the risk carried by ADHD alone and the risk associated with these other factors, in order to gain insight into which risk-factors should be targeted in preventive interventions. Therefore, it is also important for studies investigating the long-term antisocial risk associated with ADHD exposure to partial out how much of the risk is carried by ADHD and how much of the risk is carried by, for example, exposure to further familial risk-factors. Due to the multitude of risk-factors, large and detailed data-sets are needed to advance the knowledge about the link between ADHD and later antisocial involvement.

1.7. AIMS OF THE DISSERTATION

Based on the review of existing studies on ADHD which are mostly of international origin, it becomes evident that there is a great need to study how frequently ADHD is diagnosed in Denmark, to analyse data from a large clinical sample of children and adolescents with ADHD, to study the mental disorders co-occurring with ADHD and to assess the long-term risk of these individuals including the identification of early relevant predictors for later antisocial involvement.

Therefore, the aims of the present dissertation are as follows:

- First, to identify how often ADHD has been diagnosed in Danish psychiatry in the period from 1995 to 2010 in the population age 4 to 65 in the Danish Psychiatric Central Research Register (DPCRR), and to identify potential underlying time-trends explaining the developments relating to sex, age and overall trends in diagnosis of mental disorders.

- Secondly, assess the prevalence of concurrent single and multiple comorbid mental disorders in children and adolescents (age 4-17 years) diagnosed with ADHD in the DPCRR during the years 1995 to 2010, and to assess if age, sex and other comorbidity impacted the prevalence findings

- Thirdly, to assess the validity of the diagnoses of ADHD given to children and adolescents in the Danish psychiatric hospitals in the years 1995 to 2005 ages 4 to 15 years via systematically scoring medical records for the presence of ICD-10 criteria for ADHD.

- Fourthly, to systematically review controlled studies with follow ups of children and adolescents with ADHD in official crime databases, and to synthesize the existing findings in a meta-analysis.

- Fifthly, to follow up the cohort validated in the third study in the Danish national crime registry to assess the long-term risk associated with childhood ADHD for criminality and to identify early risk and protective factors for later conviction.

Each aim was assessed in individual studies and the methods and results were presented in individual papers. In the following two chapters, the methods and results of these studies are summarised.

CHAPTER 2. METHODS

The present dissertation is based on five studies, which used three different sources of data. Study I, II, and V were based on Danish registry data. Study III used a combination of register data and data from patient files. Danish register-based studies use recorded data from the public and private sectors such as data from the hospitals, pharmacies, and the justice system. As this data is recorded for administrative and not for research purposes, the number of variables available for research studies are limited. However, Denmark fortunately has a long-standing tradition for recording a wealth of details on its citizens for many years. The registers are nation-wide, the information is generally of high quality, and micro-data is available for institutions authorized to handle data by the Danish authorities. Data from the various registries can be linked to each other via the unique 10-digit personal identification number given to Danish citizens at birth and following them through-out their life [116]. Therefore, the data can be used to track groups of individuals across registries and time and can be organized in a multitude of ways to answer relevant research questions. Figure 2 provides an overview of the samples used in the four studies based on registry data. Each sample was nested in preceding samples.

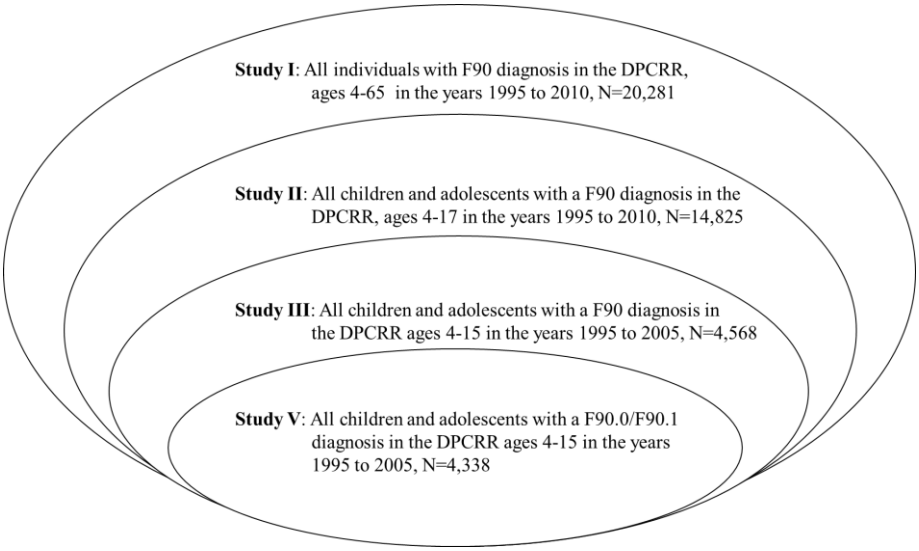

Figure 2 Sample definitions in Study I, II, III, and V

Study IV was a systematic review and meta-analysis. In a systematic review online data-bases are searched using predefined strings of search-words to identify relevant studies on specific subjects [117]. High quality systematic reviews are superior to selective reviews because the design is transparent and results reproducible [118,119]. Results from systematic reviews can be used for meta-analyses where information from individual studies identified in the systematic review is extracted, pooled and analyzed statistically [117]. The advantage of meta-analyses is that via pooling findings from individual studies the sample size is increased which improves the statistical power and thus the certainty we can have in an estimate. Study IV was used in the planning of Study V by identifying and synthesizing what is already known on the topic of antisocial outcomes of ADHD, but also by identifying caveats in the existing literature that could be full or partially compensated for in Study V.

The following section will briefly outline the designs, samples, and statistical analyses of each study, along with the rationale for nesting each consecutive sample in the preceding.

2.1. STUDY I

2.1.1. DESIGN

The purpose of this study was to identify the number of new cases diagnosed with ADHD in Danish psychiatry across the ages 4 to 65 years during the years 1995 to 2010 per 100,000 inhabitants in Denmark. The analyses were adjusted for sex and age and time-trends for the two sexes and the age-groups were identified. An additional purpose of the study was to adjust the time trends of diagnosed ADHD for the general trends in the population seeking assessment and treatment in Danish psychiatric hospitals, in order to elucidate whether the time trends in incidence rates of diagnosed ADHD were fully or partially explained by more general societal changes.

2.1.2. DATA SOURCES

The study used data from the DPCRR. The DPCRR collects data on diagnoses, contact dates, and location of the services provided from all public psychiatric hospitals. The DPCRR has collected data electronically since 1969 [120]. The DPCRR only started to collect data on outpatient activities from 1995. Data on the number of individuals living in the population of Denmark during the observation period was

obtained from Statistics Denmark which was used as the denominator to calculate the incidence rates per 100,000 person years (PY) and to age- and sex standardise the findings.

2.1.3. SAMPLE

Incident cases of diagnosed ADHD

The DPCRR was used to identify all individuals registered with an ICD-10 defined (F90.X) or ICD-8 defined (308.3) diagnosis of ADHD. All cases with a first time registration of ADHD prior to 1995 in either the ICD-8 or ICD-10 period were excluded as the DPCRR only started recording out-patient contacts in 1995.

Incident cases with any psychiatric disorder

A first time diagnosis of any psychiatric disorder was also defined using DPCRR data and was defined as an individual having an ICD-8 diagnosis of 290.X-315.X or any ICD-10 F-diagnosis of substance use disorder (F1X), psychosis or schizophrenia (F2X), affective disorder (F3X), anxiety disorder, phobia, OCD or reactions to severe stress (F40.X to F43.X), eating disorder (F50.X), ASD (F84), or ODD/CD (F90.X-F91X). The inclusion and exclusion criteria for the group of individuals diagnosed for the first time with any psychiatric disorder were identical to the criteria for the ADHD sample.

The Danish population

As mentioned above, the denominator was the general Danish population alive and aged 4-65 during the years 1995 through to 2010. The number of individuals alive in each age group split by sex was obtained for each year from records of Statistic Denmark.

2.1.4. ETHICS

The study was approved by the Danish Data Protection Agency, the Danish State Serum Institute, and Statistics Denmark.

2.1.5. STATISTICAL ANALYSES

Incidence rates per 100,000 PY of diagnosed ADHD were calculated and standardised for sex and age. For the age-standardisation and identification of time-trends the following age-strata were formed: preschoolers (age 4-5 years), school-aged children (age 6 to 12 years), adolescents (age 13 to 17 years), young adults (age 18 to 29 years), and adults (age 30 to 65 years). In addition to these figures, the

incidence rates were adjusted for the general trend for seeking assistance from psychiatric services for any psychiatric disorder.

The time-trends in incidence rates of diagnosed ADHD were assessed by fitting data-points for each year to linear functions and identifying significant periods of change (join-points) during the years 1995 to 2010. The analyses were run using SPSS 19th version [121], Stata 11th version [122], and Joinpoint version 4.0.44 [123].

2.2. STUDY II

2.2.1. DESIGN

The aim of Study II was to establish the prevalence of concurrent psychiatric disorders in all children and adolescents diagnosed with ADHD (F90.X) in the DPCRR using a cross-sectional design. Concurrent psychiatric comorbidity was defined as a mental disorder diagnosed in the time periods either three months prior to the ADHD diagnosis, at the same date as the ADHD diagnosis, or three months after the first time-diagnosis of ADHD (Figure 3).

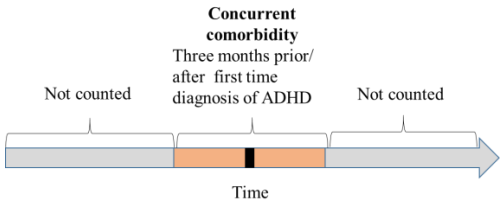

Figure 3 Definition of concurrent comorbidity

2.2.2. DATA SOURCES

This study used the DPCRR as the source of information on psychiatric disorder concurrently comorbid with ADHD. For a description of the DPCRR see section 2.1.2.

2.2.3. SAMPLE

In this study, the subset of cases identified as incident cases of ADHD from Study I aged 4 to 17 years during the years 1995 to 2010 was selected. The selection criteria for this sample are available in section 2.1.3.

2.2.4. ETHICS

The study was approved by the Danish Data Protection Agency, the Danish State Serum Institute, and Statistics Denmark.

2.2.5. STATISTICAL ANALYSES

The prevalence of the concurrent psychiatric diagnoses within the ADHD sample was calculated for the range of mental disorders displayed in Table 3. Descriptive and inferential statistics were used to describe the sample. Mann-Whitney U-tests for differences were used to calculate differences among males and females on continuous but non-normally distributed data. Chi-square tests were used to test for differences among males and females for categorical variables.

To test whether or not the prevalence of mental disorders differed between the sexes, crude and age-adjusted logistic regression analyses were performed to estimate odds-ratios (OR) with 95% confidence intervals (95% CI) associated with male sex. To test whether having one kind of mental disorder significantly increased the risk for other mental disorders, logistic regression analyses were used to estimate whether for example, comorbid ODD/CD significantly increased the risk of concurrent comorbid substance use disorders. Associations among comorbid disorders in the entire sample were only investigated in disorders with a prevalence of at least 5% and within strata (e.g. ADHD with comorbid ODD/CD) associations were only investigated for disorders with a prevalence of at least 2% within this stratum to ensure that enough observations were present. These analyses were stratified on sex and controlled for age. Analyses were performed using SPSS 19th version [121] and Stata 11th version [122]. In all tests, the alpha level was set to 0.05.

Table 3 ICD-10 definitions of comorbid psychiatric disorder for Study II

Comorbid disorders by ICD-10 code	
Affective disorders	F30-F39
Anxiety disorders	F40–F41, F93.0-F93.2
Attachment disorders	F94.X
Autism spectrum disorder	F84.X (minus F84.2)
Bipolar disorder	F30.X-F31.X
Conduct disorder/oppositional defiant disorder	F90.1, F91.X-F92.X
Depression	F32.X-F33.X, F92.0
Disorder of language, learning and motor skill development	F80.X-F83.X
Eating disorders	F50.X
Elimination disorders	F98.X-F98.12
Intellectual disability	F7X.X
Obsessive compulsive disorder	F42.X
Personality disorders	F60.X-F62.X
Reactions to severe stress	F43.X
Schizophrenia/psychosis	F2X.X
Substance use disorders	F1X.X
Tic disorder/ Tourette syndrome	F95.X

2.3. STUDY III

2.3.1. DESIGN

The purpose of Study III was to assess whether or not there was sufficient clinical data to support the dissertation that children and adolescents age 4 to 15 years diagnosed with ADHD in the DPCRR in the years 1995 to 2005 fulfilled the diagnostic criteria for this disorder according to ICD-10 criteria. To validate the diagnoses in the DPCRR a subsample of those children and adolescents were selected and the medical records for these participants were retrieved and scored for the presence of symptoms of both ADHD and CD/ODD. All child-and adolescent psychiatric clinics in Denmark agreed to participate in the study. To ensure that the assessments' were reliable a subsample were assessed by one of two co-raters, both trained clinical child and adolescent psychiatrists, and the degree of agreement was calculated.

2.3.2. DATA SOURCES

The DPCRR [120] was used to sample the participants. For the purpose of validating the diagnoses, medical records of the random subsample were retrieved. To arrive at an impression about the characteristics and functioning of the child or adolescent, a broad range of material from the medical records pertinent to the contact leading to the first time diagnosis of ADHD of the patient were included.

All the information was registered in a predefined registration form. The material reviewed by the co-raters was blinded for the child's discharge diagnosis.

2.3.3. SAMPLE

As described above, the sample consisted of children and adolescents aged 4 to 15 years diagnosed with ADHD (F90.X) during the years 1995 to 2005. The reasons for studying the validity in this subsample of the entire cohort of children and adolescents registered with ADHD in the DPCRR were the following. The decision was made to assess the validity of the ADHD in this age-group during those years as the validated cohort would be used in longitudinal follow-up studies to study the long-term effect of ADHD on development. The decision that children and adolescents could not be diagnosed later than age of 15 years to be considered for this study took into consideration the fact that the follow-up study (Study V) aimed to follow-up the children before they entered their major years at risk for antisocial involvement. As the legal age in Denmark is age 15 years, adolescents diagnosed later were excluded. Only cases diagnosed during the years 1995 through 2005 were validated to allow for sufficient follow-up time of the sample in the outcome study.

A total of N=4,568 children and adolescents fulfilled the inclusion criteria. Using the formula for sample size determination to estimate a population proportion with specified absolute precision, it was decided to randomly select a subsample of 387 children and adolescents to be part of the validation sample using the formula for [124]. For the assessment of inter-rater reliability a random subsample was drawn allowing the study to be able to detect a kappa-coefficient (K) of 0.7-0.8 [125]. To reject the null-hypothesis (K=0.4) with alpha set a 0.05, at least 68 patients would be needed. As it was uncertain how many medical records could be found and included in the inter-rater reliability assessment, a conservative number of 108 patients were selected. Five of these cases were used to establish consensus among raters about the procedures in the study and thus, the final inter-rater reliability study included 101 participants.

2.3.4. ETHICS

The study was approved by the Danish Data Protection Agency, the Danish State Serum Institute, and the Authority for Patient Safety at the Danish Health and Medicines Authority.

2.3.5. STATISTICAL ANALYSES

The sample was described using descriptive statistics including counts, percentages, means, and SDs. To ascertain the representativeness of the random samples, a series of inferential statistics including chi-square tests and independent t-tests were used. To ascertain whether any factors predicted poorer validity such as comorbidity of the child, year of diagnosis or subtype of ADHD, logistic regression analyses were performed calculating ORs with 95% CI. The alpha-level was set at 0.05. To ascertain the inter-rater reliability, un-weighted kappas were calculated [126]. Data was analysed using SPSS 22nd edition [127].

2.4. STUDY IV

2.4.1. DESIGN

The purpose of this study was to assess the long-term risk associated with having ADHD in childhood for arrests, convictions, and incarcerations in a systematic review and subsequent meta-analysis. To identify studies, electronic databases were searched using a range of MeSH, index and free-text words on the 15th of August 2015 (see section 2.4.2). Studies were selected by one person using an a priori set of in- and exclusion criteria.

The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [118]. To assess the quality of included studies, the Newcastle – Ottawa Quality Assessment Scale Cohort Studies scale (NOS) was used [128]. All included studies were quality assessed by two raters independently of each other.

2.4.2. DATA SOURCES

To identify studies, the electronic databases Pubmed, Embase and PsycINFO were searched. The following words were used in the search-string: Attention deficit, attention deficit hyperactivity disorder, minimal brain dysfunction, hyperkinetic syndrome, hyperkinetic disorder, ADHD, DAMP, hyperactive. The databases were searched for the following words to identify antisocial outcomes: crim*, incarcerat*, imprison*, delinq*, offense*, conviction*, antisocial, arrest, felon*. To limit the search to follow-up studies the following words were used in the search string: followup, follow up, longitudinal*, outcome*, prognosis, course*, prospectiv*, long term. In the search string, no constraints on year of publication, publication type, or language were used.

2.4.3. ETHICS

As this study included no direct or indirect contact with any human or live beings, no ethical or data-protection approvals were needed.

2.4.4. STATISTICAL ANALYSES

In the meta-analysis the risk-ratio (RR) and 95% CI associated with childhood ADHD for arrests, convictions and incarceration was estimated using random effect models. Heterogeneity was assessed using the Cochranes Q-statistic and I^2. Results from the quality assessment of studies was used as a co-variate in meta-regression to estimate whether study quality was significantly related to the estimated risk of arrest, conviction, and incarceration. Due to the small number of studies included, publication bias was not assessed using funnel-plots but rather by the Classical Fail-Safe N and Orwins Fail-Safe N to identify how many unpublished studies needed to exist in order to change the significance of the findings from the meta-analysis. Analyses were performed using the Comprehensive Meta-analysis (2^{nd} ed.) program [129].

2.5. STUDY V

2.5.1. DESIGN

This study was a longitudinal register-based follow-up study estimating the risk of criminality associated with the diagnosis of ADHD in childhood. Apart from estimating the prevalence for long-term arrest, conviction, and incarceration associated with a childhood ADHD diagnosis, the aim of the study was to identify

adverse and protecting factors associated with long-term conviction. To identify risk-factors, a range of child, social and family parameters were investigated.

2.5.2. DATA SOURCES

Using the Danish Civil Registration (DCR), data from the DPCRR, the Danish National Patient Register (DNPR), the Danish Prescription Register (DPR), Danish Medical Birth Register (DMBR), The Danish Cause of Death Register (DCDR), and data on educational and other background variables from Statistics Denmark were linked. The outcome was assessed using the Danish Central Criminal Register (DCCR).

2.5.3. SAMPLE

Exposed (ADHD) participants were included using the same definitions as in Study III. Based on the findings from Study III, individuals diagnosed with F90.8 and F90.9 were excluded. All exposed participants were matched on date of birth and sex, with three to five randomly selected children and adolescents from the general population of Denmark who had not previously received a diagnosed of or been treated for ADHD.

2.5.4. ETHICS

The study was approved by The Danish Data Protection Agency and The Danish Health and Medicines Authority. All information on included individuals was anonymised.

2.5.5. STATISTICAL ANALYSES

The data was analysed descriptively and by using inferential statistics such as chi-square analyses and independent samples t-tests. To estimate the risk of long-term conviction associated with ADHD exposure, crude and adjusted Cox Proportional Hazard models were performed estimating a hazard ratio (HR) and 95% CI. In these models, the cohort was followed from date of birth until the outcome of interest occurred, the person died, or to the 31st of December 2015. Data were analysed using Stata 12th edition [130].

CHAPTER 3. SUMMARY OF FINDINGS

3.1. STUDY I

During the years 1995 to 2010 in the Danish population aged 4 to 65 years a total of 20'281 children, adolescents and adults were diagnosed with ADHD for the first time. In comparison, a total of 249'607 members of the Danish population were diagnosed with any psychiatric disorder.

During these years the diagnosed incidence of ADHD increased from 7.3 to 91.2 per 100.000 PY. Adjusting the incidence rates for the time-trends observed for any psychiatric disorder resulted in a less pronounced increase from 7.3 to 53.8 per 100.000 PY. The Join Point regression analyses suggested that despite the male predominance observed for diagnosed ADHD, the increase in incidence rates had been more pronounced for females (average annual percent change (APC)= 31.7) than in males (APC=20.2). The most pronounced time-trends in diagnosed ADHD was seen in young adults (APC=46.3), in adolescents (APC= 29.3), and in adults (APC 25.2), while the APC was the least pronounced in preschoolers and school age children (for both APC=16.1). This observation remained present, but less pronounced, after adjusting the time-trends for the overall increase in the number of individuals seen in psychiatry.

3.2. STUDY II

In the 14, 825 children and adolescents diagnosed with ADHD for the first time during the years from 1995 to 2010, 52.0% had at least one other comorbid psychiatric disorder diagnosed concurrently with ADHD, and 26.2% were diagnosed with two or more concurrent psychiatric disorders. The most frequently diagnosed concurrent psychiatric disorders were ODD/CD (16.5%), specific disorders of language, learning and motor development (15.4%), ASD (12.4%), ID (7.9%), tic disorders (4.8%) and attachment disorders (4.1%). Substance use disorders, psychotic disorders, affective disorders, anxiety disorders, OCD, eating disorders, personality disorders, and elimination disorders were diagnosed in less than 2% of the sample.

When the analyses were adjusted for the age-difference observed between males and females, male sex was associated with a significant increased risk of specific disorders of language, learning and motor development, ASD, ODD/CD, and tic disorders. The risk associated with male sex was significantly decreased for psychotic

disorders, affective disorders, anxiety disorders, OCD, reactions to severe stress, eating disorders, personality disorders, ID, and attachment disorders.

The analyses of age at first diagnosis found that the mean age of diagnosed ID, specific disorders of language, learning and motor development, ASD, attachment disorders, tic disorders, and elimination disorders were before age 10 years in both males and females. Psychotic disorders, affective disorders, anxiety disorders, OCD, reactions to severe stress, eating disorders, personality disorders, and ODD/CD had a mean age of first diagnosis between the ages 10 to 15 years in both sexes, while substance use disorders were the only disorders with a mean age at first time diagnosis above the age of 15 years.

Logistic regression analyses revealed that certain disorders tended to aggregate. For example, ADHD with comorbid ODD/CD increased the risk of also having co-occurring substance use disorders, attachment disorders, and elimination disorders in both males and females.

3.3. STUDY III

Among the children and adolescents diagnosed with ADHD for the first time at age 4 to 15 years in the period 1995 to 2005 a random sample of 387 was selected for the validation study. There were no significant differences between the total sample and the randomly selected sample with respect to age, sex, region of diagnosis, year of diagnosis, subtype of ADHD, or comorbidity distributions. It was possible to identify full or partial medical records for 372 children and adolescents.

In 93.8% of these 372 files the child's developmental history was described, in 82.5% the child had been subjected to a medical examination, in 96.5% the child had been psychologically tested and in 71.2% professional observations had been made of the child in for example, the child's school or kindergarten. In 61.3 % ADHD specific questionnaires had been used as part of the assessment, and in 5.9% the child or parent of the child had participated in a structured diagnostic interview.

In 323 of the 372 cases (86.8%) the child was evaluated to fulfill the diagnostic criteria for ADHD, while in 30 out of 372 cases (8.1%) a diagnosis could not be confirmed. Out of these unconfirmed diagnoses, in 14 cases (3.8% of the sample) the diagnosis in the patients discharge letter was incongruent with the diagnosis in the DPCRR and thus, represented registration errors. In 16 cases (4.3%) the primary rater arrived at a different diagnosis or no diagnosis at all, to what the originally diagnosing clinicians had arrived at. Finally, in 19 out of the 372 cases (5.1%) there was too little

information in the patient record available to arrive at a conclusion. Year of diagnosis, comorbidity, or region of diagnosis, was not significantly related to the odds ratio of non-confirmed diagnosis. However, being registered with the F90.9 subtype of ADHD increased the odds of non-confirmed diagnoses.

While the validity of ADHD diagnoses was high in general, it was judged that the diagnoses of the subtypes held less validly in those with a confirmed ADHD diagnosis. More cases were judged to fulfill criteria for F90.1 in the validation study compared to what had been registered in the DPCRR (43.3% versus 15.9%). However, among those registered with F90.1 in the DPCRR, 41 out of 59 cases (69.5%) could be confirmed in the validation study. Agreement was established among raters in 96% of the cases (κ=0.8, p>0.001).

3.4. STUDY IV

In the systematic literature search in Pubmed, PsycINFO and Embase 11 studies, could be included [9,11,14,111-113,131-136]. These studies covered nine unique, non-overlapping samples including a total of 15'442 individuals with childhood ADHD that had been followed longitudinally. Four of the studies were carried out in the US [9,14,112,131], one was from Australia [136], one from Sweden [133], one from Finland [134], one from China [135], and one was from Denmark [113]. The ADHD diagnosis was based on DSM-II criteria in two studies [9,134], one cohort was based on DSM-III criteria [112], two cohorts were based on DSM-III-R criteria [14,131], and two cohorts were based on DSM-IV or ICD-10 criteria [135,136]. The Danish study was initiated when ICD-8 criteria were in use and included only stimulant treated children [113], while the Swedish study had used ICD-8, ICD-9, and ICD-10 diagnoses in their follow-up study [133].

Findings from the meta-analysis revealed that childhood ADHD was associated with a significantly higher risk of long-term arrest (RR 2.2, 95% 1.3-3.5), conviction (RR: 3.3, 95% CI: 2.1-5.2), and incarceration (RR= 2.9, 95% CI 1.9-4.3). For the two outcomes of arrest and conviction there was evidence for substantial heterogeneity (arrest: I^2=58.7; conviction I^2=97.2), while the test for heterogeneity was non-significant for the outcome of incarceration but still the findings were moderately inconsistent (I^2=28.7). Six out of nine included studies reported on the various type of criminal offenses [9,11,113,131,134-136], but as this reporting was not consistent across studies, no attempt was made to include these findings in a meta-analysis.

Individuals with childhood ADHD were most frequently involved in crimes of a reactive and impulsive character such as assaults, theft, substance use related crimes, and possession of weapons. There was evidence to suggest that ADHD was

associated with an earlier age of onset of antisocial involvement and an increased risk of recidivism.

In the quality assessment, the two independent raters agreed on 91.4% of items yielding a kappa of 0.7. Study quality was not significantly related to the RR for arrest, conviction, or incarceration. The result of the publication bias analyses provided evidence that the findings were not substantially affected by publication bias.

3.5. STUDY V

A total of 3,920 participants with ADHD, 18,031 participants without ADHD and data from 21,924 parent pairs were included in the study. At the end of the follow-up period, the mean age of exposed was 20.7 years (SD=3.6) and for non-exposed 21.0 (SD=3.6) years (p=0.804). A total of 79.2% of exposed participants had been treated with ADHD medication during the observation period. The exposed participants had significantly elevated levels of risk-factors across all background factors. For example 30.0 vs. 0.5% had comorbid CD/ODD, an increased number had been placed in foster care (8.9 vs. 1.3%), fewer had completed high-school (29.2 vs. 77.0), fewer had parents that had lived together for the first ten years of their life (41.3 vs. 68.1%), more came from homes with an income below the 50th percentile (64.4 vs. 50.0%), and more had either a mother (4.5 vs. 1.7%) or a father (21.1 vs. 10.1%) that had been incarcerated during the child's lifetime.

Childhood ADHD was associated with a significantly higher prevalence of having ever been charged (38.1 vs. 22.5%), convicted (34.4 vs. 19.9%) or incarcerated (17.6 vs. 6.0%). ADHD exposure was associated with a significantly higher risk of committing all types of offenses investigated in the study, except for murder and violation of tax laws. ADHD exposure was associated with having multiple convictions (21.5 vs. 8.5%) and incarcerations (10.0 vs. 2.8%).

The unadjusted risk associated with ADHD exposure for conviction was HR=2.0 (95% CI=1.9-2.2) and significantly higher for females (HR=3.4, 95% CI=2.7-4.4) compared to the estimate for males (HR=2.0, 95% CI=1.9-2.1). After adjusting the analyses for the effect of sex, presence of anxiety/depression, ID, ASD, CD/ODD, tics/Tourette, birthweight, family income, parent civil status, number of children in the household, degree of urbanisation, placements outside the home, parental education, parental ADHD, parental psychopathology, parental incarceration and parental death, the risk attributed to ADHD dropped to HR=1.5, 95%, CI= 1.3-1.6. After rigorous statistical control ADHD exposure in females was still associated with

a significantly higher risk of later conviction (Males: HR=1.5, 95% CI= 1.3-1.6, Females: HR=2.3, 95%, CI=1.6-3.5). Male sex, comorbid CD/ODD, parental separation, the number of children in the household, placements outside the home, an income below the 50th percentile, parental psychopathology, having parents that had not completed formal education, parental incarceration and parental death significantly increased the risk of conviction. Comorbid ASD, ID, and actively taking ADHD medication, reduced the risk of conviction significantly.

CHAPTER 4. DISCUSSION

The overarching aim of this dissertation was to enhance our knowledge of children diagnosed with ADHD and treated in Danish child and adolescent psychiatry. First, the analyses revealed that during recent years ADHD had been increasingly diagnosed across both sex and all age groups (Study I). Secondly, psychiatric comorbidity was frequent in children and adolescents with ADHD (Study II) and in comparison to children and adolescents without ADHD (Study V), those affected by ADHD were more likely to have comorbid psychiatric disorders and an aggregation of psychosocial risk factors (Study V). The individual risk of a patient for a given psychiatric comorbid disorder was related to the age and sex of the child, and certain comorbid psychiatric disorders tended to aggregate with each other (Study II).

Among children and adolescents with a registered diagnosis in the DPCRR it was found that a diagnosis of ADHD could be confirmed in the majority of the cases registered with ICD-10 – diagnoses F90.0 and F90.1 but also that comorbid ODD and CD may have been underdiagnosed in this population (Study III). The result of the systematic review and meta-analysis provided evidence that ADHD is associated with a two to three fold long-term risk for arrest, conviction, and incarceration, but the study also revealed important limitations in the existing body of research in this area (Study IV). The long-term follow-up study of children and adolescents with and without ADHD in the national, Danish registries confirmed the finding of an increased risk for crimes in association with ADHD, and extended the existing knowledge by identifying clinically relevant and early manifesting risk and protective factors associated with long-term conviction (Study V).

In the following sections, the findings from Study I-V and their implications will be discussed and in closing, the limitations of these studies will be described.

4.1. DIAGNOSED ADHD IN THE DANISH POPULATION

Study I found that a total of 20, 281 individuals in the age-range 4 to 65 years and alive in 1995 to 2010 were diagnosed with ADHD in Danish public psychiatric hospitals [23]. Similar to findings from other studies [15-18,21,22], the findings showed that the number of participants diagnosed or treated with ADHD has risen continuously over the last 16 years in Denmark. These general observations have attracted the attention of both Danish and international media and there have been speculations that either ADHD may have become an over-diagnosed disorder, or that more individuals than ever are developing ADHD. As the findings from Study I are merely

calculations of the number of new persons that are diagnosed for the first time with ADHD for each year, the study cannot make claims about causation or clearly explain the exact causes of why we have witnessed these trends.

However, the findings from Study I can be compared to the knowledge compiled from previously conducted studies on this topic allowing us to ascertain whether the incidence rates of diagnosed ADHD in Denmark are similar to findings from other countries. As only one other study, based on Taiwanese data, [16] on incidence rates of diagnosed ADHD has been carried out world-wide, comparisons are hampered. An alternative approach is then, to express the results of Study I differently, as a life-time risk of diagnosed ADHD, as it would allow for cautious comparison with studies assessing the life-time prevalence of ADHD. The children born in 1995 were the first birth-cohort in the dataset with complete follow-up data available in the ICD-10 period and will here be used as an example. According to census data from Statistics Denmark, 69,771 children were live born in 1995. In 2010, when the 1995 birth-cohort was aged 15 years, a total of 1,132 had been diagnosed with ADHD according to data from the DPCRR. If one assumes that all members of the 1995 birth-cohort were alive at age 15 years in 2010, this would result in an administrative life-time risk at this age of 1.6% diagnosed ADHD.

The US-American National Comorbidity Survey-Adolescents Supplements (NCS-A) investigated the life-time prevalence of mental disorders using the World Health Organization Composite International Diagnostic Interview (CIDI) in a representative community sample of adolescents aged 13 to 18 years in a total of 10,123 participants and found a life-time prevalence of ADHD of 8.6% among adolescents age 15 to 16 years [137]. Although life-time prevalence and life-time risk are not completely identical measures these can with some assumptions be compared, and by comparing the two estimates it becomes clear that the life-time risk of diagnosed ADHD in the Danish 1995 birth-cohort was rather low. Thus, despite an increasing incidence rate of diagnosed ADHD in the Danish population in the years 1995 to 2010 there is no direct evidence to support the notion that ADHD is over-diagnosed, at least not up to the end of the study in 2010. However, one cannot ascertain whether further participants with ADHD may have been diagnosed outside the public psychiatric hospitals, as privately practicing doctors are exempted from reporting to the DPCRR. However, at least within the public psychiatric system, the increasing rates of diagnosed ADHD more readily point towards a trend of increasing rates of diagnosed ADHD which may be due to improved recognition rather than over-diagnosis. Perhaps even more importantly, the results may also suggest that a substantial proportion of the Danish population of all ages may have undetected ADHD.

The other concern mentioned in this context was the notion of whether the observed time-trends can be interpreted as the result of a rising number of people developing ADHD. The results from Study I do not provide an answer to this question because data from the DPCRR can only be used to measure the frequency of diagnosed ADHD. If one wishes to gain knowledge about changing rates of ADHD in the Danish population, one would need solid population-based estimates of how frequent ADHD is in the population, independently of whether the condition has been diagnosed or not, and additional follow-up analyses could then assess whether the prevalence has truly changed over time. Such an approach can only be done by using other research designs where screening and/or a systematic diagnostic assessment of ADHD in representative population-based samples is carried out, as many factors such as better knowledge or recognition of ADHD may contribute to changes in how many affected participants are diagnosed, and therefore registered in the DPCRR. However, a recent meta-analysis of 135 studies carried out over three decades concludes that there is no data to suggest that more individuals are affected today by ADHD compared to 20 years ago [138]. This study identified some variation in findings but most of the observed variation was explained by methodological differences in studies, such as changes in the diagnostic criteria for ADHD [138].

As the present study only looked at diagnosed ADHD in the Danish ICD-10 period, the increase in diagnosed ADHD cannot be directly explained as a consequence of changed classification systems as was observed in the aforementioned meta-analysis. However, it may still be reasonable to interpret the increased incidence rates of diagnosed ADHD in Study I, at least to some extent, as a result of better recognition of ADHD in Denmark. This may have resulted from changing the diagnostic classification from ICD-8 to ICD-10 in 1994. Before 1994, a formal clinical description of ADHD did not exist in the nomenclature used in the clinics. A diagnosis of *Hyperkinetic reaction in childhood* was listed in the ICD-8 but without specifying any criteria for the condition. This background scenario may have been particularly relevant for explaining the increases in incidence rates observed for adolescents and adults. It may well be that among those who were adolescents and adults in the observation period 1995-2010, problems of inattention, hyperactivity, and impulsivity may have been overlooked when these participants were still in their childhood years due to the absence of appropriate diagnostic descriptions.

Furthermore, the study found that the time-trends in incidence rates of diagnosed ADHD was more pronounced in females compared to males, suggesting that ADHD may also have been overlooked in females. Although it is not a new finding that females may suffer from ADHD, the ADHD child prototype for many years was of a male child. However, as knowledge about ADHD in females has improved during

the recent years and organizations such as the Danish ADHD Association have done a lot of work on raising awareness of ADHD in females, these changes may ultimately have lead to less biased referral patterns for the two sexes, and contributed to the time-trends observed in Study I. Improved knowledge about ADHD and mental health problems in the general population may also help to explain the increase in incidence rates of diagnosed ADHD in terms of more people seeking help for psychiatric assessment and treatment. A German survey with assessments at two time-points with an eight year interval has for instance, found that mental health literacy has increased over time [139].

Thus, one may conclude that a major part of the increase in incidence rates observed in Study I may be explained by the concequences of introducing a new diagnostic criteria in 1994, and by the improved knowlegde about ADHD and perhaps mental disorders in general in Denmark. It is a well-known finding from epidemiological studies on incidence rates of cancer that new knowlegde and new techiques affect disease detection rates. For example, the introduction of new population-based screening techniques has been known to cause a rapid increase in incidence rates of diagnosed cancer, which later declined again once the bulk of unidentified cases became identified [140]. However, it is uncertain whether or not one may also expect such a drop in incidence rates in diagnosed ADHD in near future. Contrary to the systematic screening employed in cancer detection programs, ADHD is not a systematically screened diagnosis in the population leading to a much slower identification of previously unidentified cases. As our interpretation of the results indicated there may still be many unidentified individuals with ADHD in the Danish population, and therefore the numbers of diagnosed individuals may continue to increase in the years to come. Although the present findings cannot rule out the possibility that ADHD or other mental disorders are not affecting an increasing part of the population, it is rather unlikely that any risk-factor could affect such specific segments of the population in such a short time that it might explain the time-trends observed in Study I.

From this discussion it becomes evident that the results from Study I cannot provide precise estimates of the frequency of ADHD in the Danish population nor can the study be used to assess the exact causes bringing about the significant time-trends observed in the study. However, one may conclude that register-based studies such as Study I can be thought of as a useful tool for surveillance that can help researchers and mental health providers. Such surveillance can be crucial for detection of social groups that for some reason do not seem to reach psychiatric services, and the discussion of specific data may moderate the public concern about for instance an over-diagnosis. In addition, studies like Study I can give politicians and service

providers a hint about how services will need to adapt and to whom, to ensure that adequate resources are available and that enough professionals are trained to help individuals in need of treatment or other assistance.

However, although ensuring that the correct number of people are receiving treatment from psychiatric service is important, ensuring that the correct individuals are diagnosed is another issue. Although it is critical for patients and their families that the diagnosis is correct, the correctness of diagnoses is also important for research studies using information about diagnoses from registries such as the DPCRR as the basis for studies. Therefore, it is also critical that apart from monitoring the number of individuals receiving treatment, resources are also invested into validating the diagnoses, as was the aim of Study III. This study found that the diagnosis of ADHD among children and adolescents aged 4 to 15 years and diagnosed for the first time with ADHD in 1995 to 2005 had a high degree of validity. In 87% of the assessed medical records the descriptions of the child were in accordance with ICD-10 criteria for ADHD and there was no effect of year or region of diagnosis on the quality of the diagnoses. The only factor that significantly predicted an increased risk of not fulfilling diagnostic criteria was if the child was registered with unspecified ADHD (F90.9) in the DPCRR. This finding makes sense as this diagnosis is usually given as a preliminary referral diagnosis only to later be substituted by a more specific diagnosis or no diagnosis at all.

Therefore, the recommendation following these findings was to exclude cases with F90.9 from any future registry based studies of children and adolescents with ADHD when using the DPCRR, as done in Study V. In addition, the results of Study III determined that the presence of symptoms of ADHD and the derived diagnosis could be reliably established since the primary rater and the co-raters agreed in 96% of the cases included in the reliability study. Another important finding in the validation study was that there was evidence to suggest that the subtype *Hyperkinetic conduct disorder* had been underdiagnosed in the clinics. This finding is of great importance for the interpretation of the findings of both Study II and Study V, and will be discussed later (section 4.4.5). Unfortunately Study III did not assess the validity of registrations for other psychiatric disorders among children and adolescents diagnosed with ADHD in the DPCRR.

4.2. THE LONG-TERM ANTISOCIAL OUTCOME OF ADHD

The results of the systematic review and meta-analysis in Study IV provided evidence that childhood ADHD was associated with a two to three fold risk for being arrested, convicted, and ultimately incarcerated due to engagement in criminal activities.

However, although these analyses provided strong evidence to support the hypothesis of an increased long-term risk for getting involved in criminality associated with childhood ADHD, the systematic appraisal and quality assessment of studies also identified some potential limitations in the existing literature related to methodological issues and representativeness of samples. These issues will be the focus of the next paragraphs and will also highlight the complexity of studying the long-term antisocial outcome associated with ADHD.

The quality assessment of studies in Study IV found that many studies had not been well-controlled or attempted to match for the effects of what Study IV considered key confounders, namely, the effect of age, sex or SES. However, as discussed in the back-ground section of this dissertation also other factors are known to increase the risk of long-term criminality (section 1.6.3), and as most studies included in Study IV included less than 300 participants, the samples have not been sufficiently large to allow for statistical control of a sufficiently large number of potential confounders, including presence of psychiatric comorbidity and differences in social and family backgrounds of children and adolescents with and without ADHD.

The importance of such methodological control in outcome studies becomes clear when we consider the heterogeneity of samples of ADHD which was evident from the results of Study II and Study V. Study II found that 52% of children and adolescents aged 4 to 17 years had at least one other psychiatric comorbidity diagnosed at the time of their first assessment of ADHD and that the rates of comorbidity differed according to the age and sex of the child. Moreover, Study II revealed that the risk of one comorbid psychiatric disorder was dependent on the presence of other disorders and as such the risk was not evenly distributed in the sample.

Furthermore, the findings from Study V highlighted the heterogeneity of ADHD samples in terms of the social and family background of these children and adolescents. These findings indicate that children and adolescents with ADHD are just as different from each other on many variables as children and adolescents are in general, but the findings also show that various risk-factors are aggregated in this population. These characteristics highlight the difficulties emerging from the study of long-term outcomes of childhood ADHD, as these children and adolescents experience an accumulation of risk-factors, which are predictive of adverse developmental outcomes. For example, independent of ADHD there is a well-known association between low birthweight and the long-term risk for receiving less education [141], and an increased risk of incarceration or substance abuse associated with childhood CD [142,143]. Therefore, when studying the outcome of ADHD, one

should ensure that large data-sets with relatively detailed data are used, such as the dataset used in Study V, to allow an adequate control for the presence of at least a matrix of common and well-known risk-factors and the age and sex of the child needs to be taken into consideration as well. Such a procedure is necessary if one wants to address with more certainty which kind of risk of criminality is specifically related to ADHD. One could argue that such an endeavor is artificial as the clinical reality, as documented in Study II and V, is marked by complexity, but then again it is important to partial out what factors cause which outcomes, if we want to identify meaningful subgroups in this patient population and ensure that the right risk factors are targeted by our interventions and prevention programs.

Important risk-factors for later conviction, which were over-represented in the ADHD sample and predictive of conviction in Study V, but were not systematically controlled for in the studies included in Study IV, included comorbid CD/ODD, parental divorce, placements outside the home, parental psychopathology, parental antisocial history, and a higher number of children in the household. Study V found that each of these factors made small but significant reductions in the estimate of how strongly childhood ADHD predicted the risk of conviction, as the hazard rate dropped from HR= 2.0 (95% CI=1.9-2.2) in the unadjusted model to HR=1.5, 95% (CI= 1.3-1.6) in the final model. Thus, a potential consequence of a lack of statistical or methodological control in the studies included in Study IV could have been that some of the excess risk for long-term arrest, conviction, and incarceration attributed to ADHD could have been confounded and the risk associated with ADHD overestimated. This information is important, as it highlights that preventive and treatment initiatives targeted at this group of children and adolescents may need to focus broader than merely controlling symptoms of ADHD to be successful in buffering the long-term risk of criminality.

Apart from the difficulties described above that makes it complex to partial out from the existing literature how much of the risk for criminality was specifically associated with ADHD, there are also critical factors that may hamper our ability to generalize findings from the previously conducted long-term outcome studies, to the samples of children and adolescents seen in the Danish psychiatric clinics today.

First, the definition of ADHD in most of the long-term follow-up studies included in Study IV were based on diagnostic criteria that in many ways are different from the current ICD-10 criteria currently in use in Denmark. As described in background section 1.3, each revision of the DSM had the implication that an increasing number of participants were above the threshold of the diagnosis of ADHD. In addition, the overlap between children diagnosed with ADHD from DSM-II to DSM-III was only

55.4% [44], and it is likely that the DSM-II had included participants in the ADHD samples who would today be classified with other disorders. The consequences could be that the antisocial outcomes of children and adolescents diagnosed with ADHD during the DSM-II and DSM-III period could be worse compared to children and adolescents diagnosed using more recent criteria. This could be the case if the children from the historical cohorts either had a more severe presentation of ADHD or to a substantial degree were misclassified cases of for example, CD. Had more studies been available for analysis in Study IV, meta-regression analyses could have provided evidence for or against this hypothesis. This procedure would have allowed us to estimate the effect of the year of the diagnosis on the relative risk of arrest, conviction, and incarceration and perhaps explain some of the substantial heterogeneity identified in the meta-analysis.

Based on the finding from Study I revealing that ADHD had increasingly been diagnosed during the years in which the participants included in Study II and V were diagnosed, one could also argue that it may have been problematic to have studied this cohort of children and adolescents with ADHD as an entire sample. It may be the case that the clinical picture in participants diagnosed with ADHD in the beginning of the observation period had been more complex or even more severe than in those who were diagnosed later on. Unfortunately, severity of ADHD was not assessed in the validation study (Study III) and such a potential time-effect was not assessed in Study II or Study V. Thus, a future study should examine whether the children and adolescents seen in the Danish psychiatric clinics with ADHD during the ICD-10 period have changed with respect to the patterns of psychiatric comorbidity, social backgrounds etc. Such a study would provide information to which degree time and cohort effects might affect the potential to use results from one time-point for projections on the prognosis of children and adolescents seen with ADHD in the clinics today.

Second, the findings from Study II and Study V also point to other domains that make the findings from some of the previously conducted follow-up studies difficult to generalise to the children and adolescents with ADHD we see in the clinics. As mentioned in the background chapter (see sections 1.5, 1.6), many previous studies conducted on children and adolescents with ADHD have systematically excluded a relatively large proportion of the children and adolescents that are seen at the psychiatric departments, namely, those with comorbid ASD, children with ID, and even children with an IQ just below 80. Study II identified that 18.4% of the sample had either ASD or ID, and in the sample of Study V 21.5 % had at least one of these two diagnoses. Thus, Study II and Study V underscore that a substantial proportion

of those children that are seen at the Danish psychiatric departments previously have not been followed up longitudinally on antisocial outcomes in other studies.

This is problematic for two reasons. First, little is known about the differential outcomes of children with ADHD with these relatively frequent comorbid psychiatric diagnoses. Study V was most likely the first study to assess this constellation of psychiatric problems and its impact on long-term conviction. Secondly, this exclusion hampers the external validity of the results of the individual studies on which Study IV was based, as Study V provided evidence that having ADHD and comorbid ASD or ID significantly reduced the long-term risk of later conviction. Therefore studies excluding these subgroups of patients may overestimate the risk of long-term antisocial development for the combined group of children and adolescents with ADHD.

Despite the limitations of Study IV, i.e. the studies included in this review, the overall finding of an association between childhood ADHD and later criminality was in accordance with the finding of Study V that childhood ADHD is a psychiatric disorder that at least for some affected individuals carries a long-term risk for criminal involvement. However the results of the adjusted models in Study V provide evidence to suggest, that the association may not be so strong as previously observed, and the findings highlight, that not all children and adolescents have an equal long-term risk. Based on these findings, it seems reasonable to conclude, that it is too simplistic to talk about an increased risk of later criminality in children and adolescents with ADHD, as this excess risk is primarily experienced by a subgroup of these patients.

Both Study IV and V found that on a group-level ADHD is associated with an increased risk of both single and repeated crime, in particular for reactive and impulsive crimes such as theft and violence. As an additional strength, Study V by extending the findings from Study IV provided evidence that ADHD is not only associated with a long-term risk for involvement in relatively frequently committed crimes, but also with the more rare and serious offenses such as rape, serious violence, and attempted murder. Since the regression analyses in Study V used *"any conviction"* as the outcome, it is still uncertain whether childhood ADHD per se is associated with the involvement in these serious types of crimes or predisposes for repeated criminal engagement.

These questions should be addressed in future analyses of the dataset. Another important future study should address the question whether or not certain clinical characteristics and specific psycho-social backgrounds are particularly predictive of

certain kinds of crimes. A study of this kind should be carried out to further nuance and improve current knowledge about who is at risk for which crime and to assist in developing tailor-made preventive strategies. In addition, as Study V was based on register-data only, it will be important to conduct large follow-up studies of children and adolescents with ADHD that also control and estimate the effect of other potentially important predictors such as neuropsychological functioning and symptom severity, as data on such variables are not available from the Danish national registries, but potentially would provide us with invaluable insight.

4.3. CLINICAL IMPLICATIONS FOR CRIME PREVENTION

All in all the findings from Study II, the critical evaluation of Study IV, and the findings from Study V highlight the complexity of studying the long-term outcome of ADHD, and that it may not be reasonable to talk about *"the outcome of ADHD"* as such. Rather, the risk of criminality associated with childhood ADHD need to be assessed in more detail taking into consideration the matrix of differential risk and protective effects on developmental pathways that could call for different approaches of treating ADHD. Knowledge of this kind could ultimately improve prevention strategies aimed at reducing the adverse long-term outcomes experienced by children and adolescents with ADHD but also help to channel economic and treatment resources to the right population of children and adolescents. The findings indicate that tailoring the intervention to the specific childs needs as proposed by so-called personalised medicine, and taking into consideration both individuals, family and broader social factors may be the most viable approach if the aim is to prevent the long-term risk for criminality.

Rather than looking at children and adolescents with ADHD as a homogenous group with the same needs, the rationale of personalised medicine models look for patient populations to be separated into different groups that require the individual adaption of clinical decisions, practices, and interventions. Personalised medicine draws on the philosophy from Hippocrates by highlighting that *"it is more important to know what sort of person has a disease, than to know what sort of disease a person has"* [144]. This is meant in no way to diminish the importance of recognising and treating ADHD per se, but is highlighted here as an alternative approach that takes into consideration a broader range of factors than merely the symptoms of ADHD. Although the results of the studies from the present dissertation cannot specifically point to definitive parameters on which to subgroup children and adolescents with ADHD, the findings from Study II and Study V in particular, provide some preliminary hints about what and who should be targeted.

First of all, it is relevant to treat ADHD. The analyses from Study V provided evidence that at least short term effects of treatment with ADHD medications help to reduce the risk of conviction by a 20-30% rate and there was evidence to support, that ADHD in itself confers a long-term risk for conviction. The protective effect of ADHD medication was not seen when patients were treated with selective serotonin reuptake inhibitors (SSRI) or antipsychotics and thus support the specific efficacy of ADHD medication on this outcome. Study V is the second study known so far to find this association after it had been described before in a Swedish registry-based study [145].

However, the interpretation of the results from Study V are also in line with the conclusions from the British NICE-guidelines that ADHD in children and adolescents should be treated by combining pharmacological with psychosocial interventions [146]. This approach seems most promising in the light of the results of Study V highlighting the heightened risk for long-term crime outcomes associated with comorbid CD or ODD. Treatment with stimulants is known to have some beneficial effects on symptoms of ODD and CD [147] but the NICE guideline clearly points out that a person - centered, family - based or multisystemic treatment program is recommended as first line treatment for the treatment of antisocial disorders [148].

These approaches are likely to work not only by targeting symptoms of CD and ODD but also by addressing other risk-factors for later crimes such as the effect of parental antisocial involvement as identified in Study V. Such programs may help to prevent crime by improving parenting skills and family functioning in socially disadvantaged families or families who are lacking important skills to manage their child and via engaging social services in the treatment program. The results of Study V underscore that it is critical to take into consideration not only the ADHD symptoms but also treat the comorbidity with CD and ODD, as well as to look at the wider family and social system in which the child´s life is embedded. Involvement of social services, employment of broader community based interventions aimed at buffering the effect of social deprivation on antisocial involvement in deprived neighborhoods, and implementation of pro-social skill development programs in institutions and schools may represent further constructive interventions. This understanding is important so that the problems associated with ADHD do not become exclusively individualised or thought to derive from ADHD alone. Furthermore, this approach also highlights that clinicians carry a high responsibility in collaboration with the wider mental health and social service system for ensuring a holistic and tailored service to children and adolescents with ADHD and their families that goes beyond only treating children and adolescents with ADHD using medications.

4.4. LIMITATIONS

While some limitations of the studies in this dissertation have already been mentioned throughout the methods section and the discussion, this final section of the discussion will briefly sum up the limitations of the various studies of the present dissertation.

4.4.1. STUDY I

One limitation of Study I pertained to the issue already mentioned in the sections above that the DPCRR only includes information about diagnoses given at the public psychiatric hospitals. Thus, the numbers of patients diagnosed by privately practicing psychiatrists and other specialists are unknown. Thus, one has to conclude that Study I and other register-based studies cannot be used to provide an accurate prevalence or incidence estimate of the number of Danes affected by ADHD, and can only provide knowledge about the number of individuals who are diagnosed or treated for ADHD. To arrive at estimates of the prevalence of ADHD in various age and sex strata in the Danish population, a community based study with screening and interviewing of the members of the population using the diagnostic criteria of the ICD-10 would be needed to be carried out.

Furthermore, since the DPCRR only started recording outpatient contacts in 1995, some diagnoses of ADHD predating 1995 could have been missed and erroneously have been recorded as incident diagnoses in the years after 1995 for participants born before 1995. Rather than having been excluded from the analyses, these individuals might have falsely inflated the findings dealing with the participants born before 1995. However, even when considering this limitation the incidence rate of diagnosed ADHD was relatively low in the Danish population. Finally, it is worth mentioning that the diagnoses of ADHD given to children and adolescents above the age of 15 or later than in the year 2005 have not been validated. This critique also pertains to the data on adults with ADHD diagnoses.

4.4.2. STUDY II

As Study II was based on the sub-sample of children and adolescents that were aged 4 to 17 and diagnosed with ADHD during the years 1995 to 2010, the limitations described for Study I also pertain to Study II. It needs to be acknowledged that the heterogeneity in psychopathology observed in Study II may not be representative for children and adolescents with ADHD in general, for those seen outside the public psychiatric hospitals or for children and adolescents with unidentified ADHD, as clinical and community based samples may differ in terms of their clinical

complexity [64]. This limitation is however, not considered essential for the present dissertation as the specific aim was to define, describe, and study the outcome of children and adolescents seen at the psychiatric departments in Denmark, but results may not fully generalise to children and adolescents with ADHD seen outside the public hospitals in private clinics or to participants with unidentified ADHD. Also, the quality of diagnoses comorbid to ADHD has not been validated. The only exception from this statement relates to the presence of comorbid CD and ODD in the participants who were diagnosed at age 4 to 15 years in the time-period 1995 to 2005. For these participants Study III, assessed the validity of the CD/ODD diagnosis and found that there was an under-recognition of this comorbidity in general, but few false positives. A problem of under identification of a range of comorbid psychiatric conditions in Study II is likely, as the prevalence estimates for a range of psychiatric comorbidities including anxiety disorder and learning disabilities were quite low, compared to findings from other studies [24,62,63,70]. This finding suggests that other comorbidities with less pronounced impact on the child's functioning or less salience may have also been missed. Therefore, the findings from Study II have to be considered as conservative estimates.

4.4.3. STUDY III

As the validity of diagnoses in Study III was assessed using only medical record material without direct interviews or assessments of the participants or their families, there is a risk that the findings from Study III were affected by a confirmatory bias. First of all, the primary rater along with the co-raters knew that they were assessing medical record from participants diagnosed with ADHD. An alternative approach would have been to also include participants without ADHD in the validation study. However, such an approach would also have limitations as it is difficult to blind patient file material and as the assessments of patients and the patient file material was heavily influenced by the clinicians´ hypotheses of ADHD. For example, the extensive use of ADHD rating scales, the assessment of continuous performance difficulties, and the initiation of treatment with stimulants would likely have broken the blinding.

Secondly, the primary rater had a strong personal interest in finding high validity of ADHD diagnoses in the DPCRR as this data would form the basis of other studies; this could unknowingly have biased ratings towards confirmation. Therefore, it was important that the records were judged by co-raters who were not using the DPCRR to study ADHD. The finding of high inter-rater reliability suggests that the bias did not substantially impact the ratings by the primary rater, but again blinding of co-raters was only partially possible. Thirdly, a definite bias in this study relates to the

fact that raters only had access to evaluating medical records written by clinicians who suspected, assessed and finally diagnosed ADHD. Thus, evidence conflicting with a diagnosis of ADHD could unconsciously have been omitted from the medical records. This would not have been a deliberate act by those writing the medical record but could either way have biased findings from the validation study towards a higher rate of confirmation.

An alternative approach that could have minimised the effects of a confirmatory bias on the results of Study III could have been to invite patients that were registered with a diagnosis of ADHD in the DPCRR for a diagnostic assessment of past and present symptoms of ADHD. This procedure was not considered for the study as it could have critical ethical complications. Some individuals might not have been aware of or remembered the fact that they as children had ever had a psychiatric assessment or that they had ADHD if their parents had not disclosed it to their children. In addition, despite the fact that retrospective assessment of symptoms of ADHD is often used when assessing adults referred and suspected of having ADHD, this approach also has limitations.

Some studies have found only moderate correlations between reports of childhood ADHD and current symptoms of ADHD in interviewed adults [149,150]. In the New York follow-up studies, individuals diagnosed with ADHD in childhood and controls were assessed in adulthood for their childhood symptoms of ADHD to assess the accuracy of the recall of symptoms [151]. This study found that among those cases that had been diagnosed with ADHD in childhood 78% endorsed enough retrospective symptoms to fulfill criteria for childhood ADHD compared to 11% of the controls. The agreement between retrospective diagnoses made at the follow-up assessment and the diagnoses given in childhood was Kappa=0.67. These results suggest that while there is a large overlap, this method is not without its flaws. However, future validation studies could opt for combining patient file material with direct assessments of current and past symptoms of ADHD interviewing both the person diagnosed with ADHD and a relative.

Finally, a limitation of this study relates to the external validity of findings. Despite the fact that great care went into designing the study to arrive at a reasonable sample size and that the validation study sample was randomly drawn from the total cohort, it is unclear whether the findings from the validation study can truly generalise to the total sample. In addition, as the study only assessed children and adolescents diagnosed from 1995 to 2005, the validity of diagnoses given later or to older participants remains unclear. The findings from Study I revealed that for each year in the study period an increased number of participants were diagnosed with ADHD

across all age and sex-strata. Thus, it is important to assess the validity of diagnoses given after 2005 in the DPCRR to ensure that the high-quality assessment observed in Study III is still carried out. Unfortunately, in recent years the Danish psychiatric departments have also been subjected to an increasing political and administrative pressure to ensure that waiting lists are cut back and that more patients are seen without expanding the services. Clinicians are more pressured to ensure that diagnoses are given faster than ever before as a consequence. These changes could have deleterious effects but the concern needs to be addressed empirically.

4.4.4. STUDY IV

Study IV differed from the remaining empirical studies in this dissertation as it was a systematic review and meta-analysis. As the purpose of the this study was to inform the design of Study V, the review and meta-analysis focused solely on studies that had employed a design similar to what was possible to mimic in Study V. Therefore, the study only focused on studies that had assessed the long-term crime risk associated with childhood ADHD using official sources of data to report on the outcomes. Thus, this study did not assess risk of involvement in self-reported crime or scores on antisocial behaviour scales. A focus only on data from official crime registries or documents can only capture the types of antisocial behaviour that come to the attention of law-enforcement agencies and thus, may only cover the "tip of the iceberg" [110]. Despite this narrow focus, the fact that the results are not affected by the biases that arise when using self-reports, such as exaggeration or under-reporting [110], is advantageous. In addition, as Study IV assessed the relative risk rather than estimated the prevalence of antisocial involvement, this bias should only have affected the findings if either individuals with childhood ADHD or controls had had an elevated risk of getting caught for their offenses.

Another limitation of Study IV relates to the methods used. In the study only one author was responsible for the selection of studies, increasing the risk of missing or leaving out studies by accident. To minimise the risk of overlooking studies, literature lists of included studies were back-searched, however; it is not certain whether or not relevant studies may have been missed. However, the publication bias analyses revealed that the results were robust and that more than 40 studies had to have been missed or unidentified in the search to change the findings to a null-finding. Finally, due to the relatively small number of studies identified for the three primary outcomes of arrests, convictions, and incarcerations, too few studies existed to explore the sources of heterogeneity that were present in the study on the risk of arrests and convictions.

4.4.5. STUDY V

As Study V was the first among the three registry-based studies in this dissertation that was based on a sample for which ADHD diagnoses were validated, there is some certainty that the rate of misclassification among the exposed was relatively low. However, as there were no measures ascertaining whether cases classified as non-affected could be taken, the risk of misclassification of the non-affected status is unknown. However, as the participants were randomly drawn from the general population and based on what is known about the prevalence of ADHD in this age-group, the rate of misclassification should not exceed some 5-10%. At best, the misclassification of this kind would tend to underestimate the risk of criminality associated with ADHD.

Secondly, and related to the findings from Study III it is likely that for example, misclassification of ODD/CD status among the child and adolescent cohort occurred. Such misclassification could both result in under- and overestimation of the effect of these variables on outcome. Thirdly, as the findings from Study I were suggestive of many years of overlooking ADHD in the population of adults in the time-period from 1995 to 2010, parental ADHD and psychiatric status could have been misclassified. Therefore, as adult ADHD is associated with adult social disadvantage, the effect of psychosocial adversity (e.g. low income, low educational status, antisocial involvement) on long-term conviction rates may have been overestimated if these were indirect measures of unidentified parental ADHD. Fourthly, a limitation of Study V was that many of the participants included in the analysis had not yet lived through all their years at risk for antisocial involvement and thus, later follow-up analyses of this cohort may find that estimates will change as the individuals of this sample grow older. Fifth and finally, as Study V was based only on register data, the effect of other measures such as neuropsychological test-performance, personality traits or symptoms severity could not be estimated nor controlled for. This is unfortunate because information on such variables may have improved our knowledge about risk-factors but also protective factors even more than was the case in Study V.

CHAPTER 5. CONCLUSION

The purpose of this dissertation was to assess how often ADHD has been diagnosed in Denmark in the ICD-10 period and to identify underlying time trends. In addition, the dissertation aimed at describing the socio-demographic and clinical characteristics of Danish children and adolescents with ADHD, to assess their long-term risk for crimes, and to analyze whether any characteristics of the children and their families during childhood and adolescence were predictive for later crimes.

Study I found that since the introduction of ICD-10 in Denmark in 1995, diagnoses of ADHD in the Danish population increased. This trend was more pronounced among adolescents, adults, and females. Despite these observed increases, there was no direct evidence to support the conclusion that this trend was caused by either over-diagnosis or an increase in the amount of individuals in the population developing ADHD. It is more likely, that the time trends were related to increased knowledge, awareness, and recognition of ADHD and mental disorders in general. The results of Study III also provided evidence that at least the diagnoses of ADHD given to children and adolescents during the years 1995 to 2005 in Danish psychiatric hospitals had a good overall validity, although the diagnoses of the subtypes of ADHD as diagnosed in the ICD-10 were less valid.

The results of Study II and Study IV did however, support that children and adolescents with ADHD do not constitute a homogenous group of patients. Rather, these patients often have other comorbid psychiatric problems, more often come from socially disadvantaged homes, and overall tend to have an aggregation of risk factors known to affect the long-term developmental outcome of children and adolescents. Study IV provided an overview of the previously published studies assessing the long-term risk associated with ADHD for having an official arrest, conviction or incarceration record and it was estimated that ADHD in childhood leads to a two to threefold increased risk of these outcomes.

In Study V, the aim was to replicate and extend these findings in a large, nationwide cohort of children and adolescents diagnosed with ADHD at the Danish psychiatric departments. This study allowed for the analysis of rigorously controlled models of the aggregation of risk factors in this patient population to an extent that had not been possible in most of the previous studies due to small sample-sizes. Even in adjusted models, ADHD in childhood was associated with an increased risk of long-term conviction. However, the results also revealed that not only ADHD but also comorbid CD/ODD, low SES, parental psychopathology, and parental antisocial involvement

were significant risk factors, that need to be targeted if later crime development in children and adolescents with ADHD should be prevented successfully.

Therefore, it was concluded that it may not be reasonable to talk about *"the outcome of ADHD"* as such but rather, that clinicians and other professionals in their attempts of treating children and adolescents with ADHD and their families need to give equal weight to assessing and intervening with comorbid conditions and social risk-factors. Only by a patient-oriented rather than a diagnosis-focused approach to treatment will the intervention efforts be likely to succeed. Future analyses of the Danish register data and further longitudinal studies, including other sources of data than is contained in the registries should aim to improve our knowledge about how the various risk and protective factors interact and how individuals with ADHD are likely to develop. As complex problems are likely to be solved only by complex solutions, we need to study this complexity and reach a better understanding of ways to change or positively impact on the developmental trajectories of at-risk children and adolescents.

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SUMMARY

The most frequent reason for referral to the child and adolescent psychiatric hospitals in Denmark is the suspicion that a child or an adolescent may have Attention-Deficit/Hyperactivity Disorder (ADHD). The purpose of this dissertation was to assess how often ADHD has been diagnosed in Denmark, to assess the validity of the ADHD diagnoses given to children and adolescents, to describe the socio-demographic and clinical characteristics of Danish children and adolescents with ADHD, and to assess their long-term risk for crimes.

In the years under investigation, the incidence rates of diagnosed ADHD had significantly increased and the majority of ADHD diagnoses given to children and adolescents could be confirmed and were given based on high-quality clinical assessments. Results supported that children and adolescents with ADHD constitute a heterogeneous group that often have comorbid psychiatric problems, and overall tend to have an aggregation of risk factors for criminality. Both the meta-analysis and analyses of the Danish data confirmed, that childhood ADHD increases the risk of long-term criminality. Not only ADHD but also comorbidity, low socio-economic status, parental psychopathology, and parental antisocial involvement were among significant risk factors for criminality and therefore a patient and family-oriented approach to treatment and prevention is warranted.

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